5727

JOURNAL OF NEUROPHYSIOLOGY

[J. NEUROPHYSIOL.]

EDITORIAL BOARD

J. G. DUSSER de BARENNE
J. F. FULTON • R. W. GERARD

JUL 14 1938
SURGICAL DIVISION

ADVISORY BOARD

E. D. ADRIAN (Cambridge)
P. BAILEY (Chicago)
P. BARD (Baltimore)
G. H. BISHOP (St. Louis)
F. BREMER (Brussels)
D. BRONK (Philadelphia)
E. VON BRÜCKE (Innsbruck)
S. COBB (Boston)
H. DAVIS (Boston)
U. EBBECKE (Bonn)
J. C. ECCLES (Sydney)
J. ERLANGER (St. Louis)
W. O. FENN (Rochester)
A. FORBES (Boston)
H. S. GASSER (New York)
R. GRANIT (Helsingfors)
W. R. HESS (Zürich)
MARION HINES (Baltimore)
DAVENPORT HOOKER (Pittsburgh)
R. LORENTE DE NÓ (New York)
W. PENFIELD (Montreal)
H. PIÉRON (Paris)
S. W. RANSON (Chicago)
G. VAN RIJNBERK (Amsterdam)
C. S. SHERRINGTON (Ipswich)

MAY, 1938

VOL. I *Issued Bi-monthly* NO. 3

PUBLISHED BY CHARLES C THOMAS
220 EAST MONROE STREET • SPRINGFIELD, ILLINOIS, U.S.A.

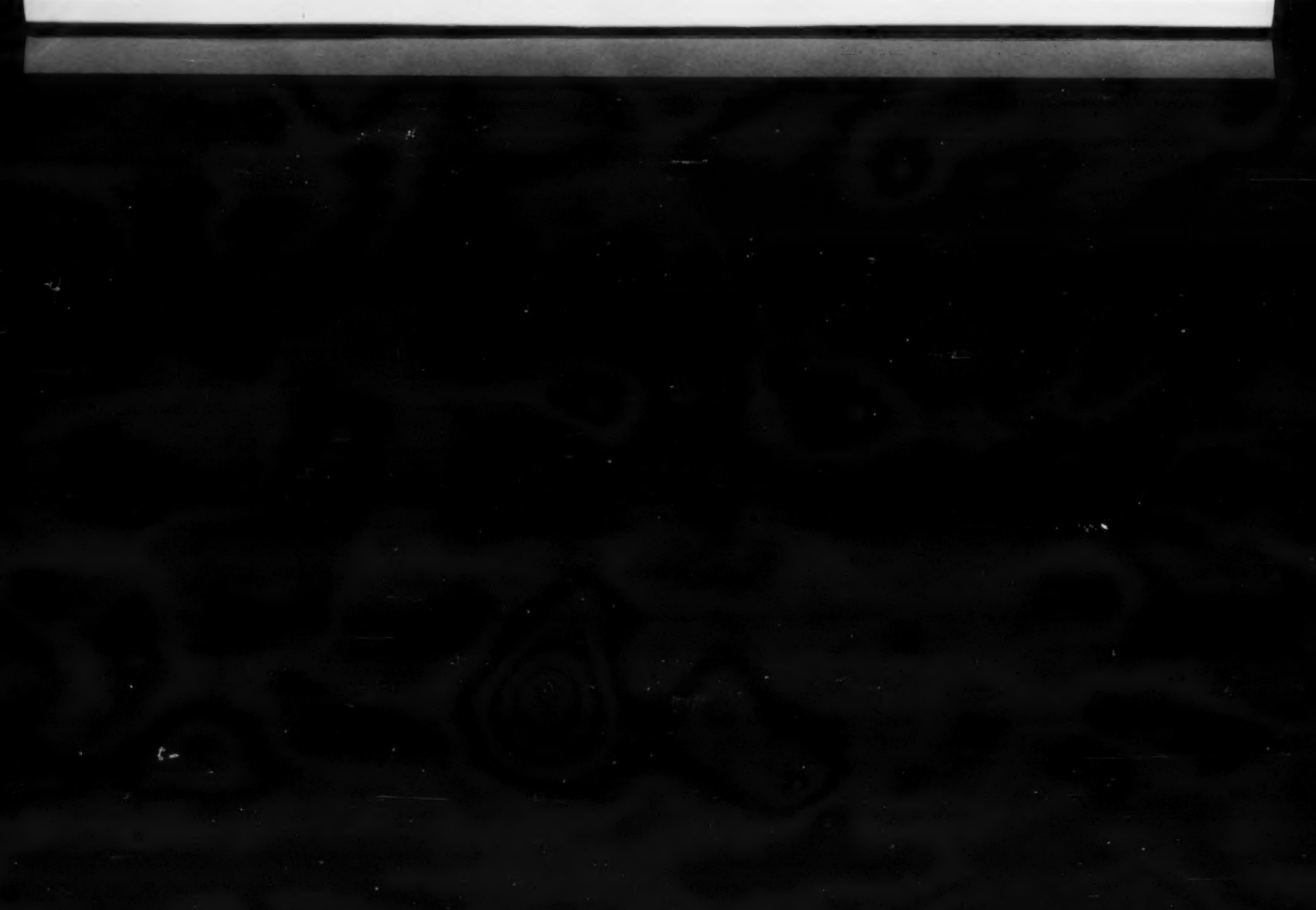
JOURNAL OF NEUROPHYSIOLOGY

SCOPE: The primary aim of the JOURNAL OF NEUROPHYSIOLOGY is to provide a channel for *prompt* publication of original work bearing on the functions of the nervous system, peripheral and central. It has been planned to embrace all aspects of the subjects amenable to experimental analysis; it will not include morphology for its own sake nor neuropathology, and only those clinical, psychological or zoological contributions will be considered which are primarily experimental in character.

EDITORIAL POLICIES: Manuscripts should be addressed to the Editors of the JOURNAL OF NEUROPHYSIOLOGY, 333 Cedar Street, New Haven, Connecticut. Manuscripts will be selected for publication in a particular issue of the JOURNAL from those which reach the Editors up to the day of publication of the preceding issue. Final selection will be made within three weeks of this day and those articles for which there is no space available in the issue in question will be promptly returned to their authors. Only for special reasons will a manuscript be held for later publication if it cannot be included in the proper issue. Manuscripts should be *concisely* written and submitted in typescript ready for publication. The list of references, footnotes, tables, protocols and any textual matter to go in small print should be submitted on pages separate from the ordinary text. A brief summary should be included and an abstract for *Biological Abstracts*. It is requested that citations include the name and initial(s) of the author(s) with the full title and pagination of the paper or book. Journal citations should be abbreviated in accordance with the system used in *A world list of scientific periodicals published in the years 1900–1933* (Oxford University Press, 1934). Citations of books and monographs should include title, publisher and date. References are to be arranged alphabetically and may be cited by year or number. Corrections in galley proof will be allowed free of charge up to 5 per cent of the original cost of composition. The cost for changes in page proof, based upon actual time consumed by the compositor, will be borne by the author. Tabular, mathematical or chemical formulae in excess of 10 per cent of composition costs can only be included at the expense of the author. A maximum of six illustrations, zinc or half-tone, each up to approximately 3 × 3½ inches in size, will be allowed free in each paper. Additional illustrations can be included at a nominal cost. All illustrations, especially photographs, should be sharp and clear, and submitted in a form adapted for immediate reproduction, i.e., lettering, mounting and arrangement of plates are to be done by the author. Reprints may be ordered on the application-blanks supplied with the galley-proof. Twenty-five reprints with covers will be issued gratis. Larger orders will be sold at cost.

SUBSCRIPTIONS: The subscription rate for the volume of 6 bimonthly issues is $6.00 in the United States, Canada and Latin America, and $6.50 in other countries; it is payable in advance direct to the publisher: Charles C Thomas, 220 East Monroe Street, Springfield, Illinois, U. S. A.

COPYRIGHT 1938 BY CHARLES C THOMAS



©C1B 382657
JUL 12 1938

LIMITS OF VARIATION OF THE SYNAPTIC DELAY OF MOTONEURONS

RAFAEL LORENTE DE NÓ
*From the Laboratories of The Rockefeller Institute for Medical Research, New York**

(Received March 21, 1938)

THE MINIMAL duration of the synaptic delay of ocular motoneurons has been determined (1935a) with sufficient accuracy, but considerable dificulties have been found in measuring its maximal duration. Experimental results (1935d) indicated that the maximal delay is not much longer than the minimal delay, and that the expected small variations could scarcely be measured in the original preparation, in which the responses were recorded from the internal rectus muscle (1935d, p. 527). A sufficient degree of accuracy has now been attained by recording the responses from the trochlear nerve.

Eccles (1936, 1937) has shown that the synaptic time in the superior cervical ganglion also is rigidly fixed within narrow limits, but it may be slightly shortened by creating facilitation or it may be lengthened by setting up refractoriness of the ganglion cells. Although in a different time scale, identical results are obtained with the trochlear motoneurons.

TECHNIQUE

The observations here reported have been made on the oculomotor preparation of the rabbit (1935a, 1938a), the responses being recorded from the trochlear nerve. The synaptic delay is calculated by subtracting from the total latency of the F response 0.7 msec., which is the conduction time of the impulses from the F electrodes to the motoneurons, plus the conduction time from the motoneurons to the recording electrodes. The latter can be determined with sufficient accuracy by stimulating the motoneurons with short induction shocks, but the former must be estimated. Since the F electrodes are placed at about 10–15 mm. from the motor nucleus, the possible error is of the order of 0.1 msec.; for this reason two figures (0.5–0.6 and 0.8–0.9) are given for the durations of the extreme synaptic delays; the true value is doubtless within the range of these figures.

RESULTS

Delivery of a shock through the F electrodes causes the arrival to the motoneurons (*M. N.*, Fig. 1, I) of an initial volley of impulses (*f*) followed by a series of volleys delayed during their passage across internuncial neurons (*i*). The temporal course of the arrival of the impulses is indicated in Fig. 1, II.

A number of motoneurons respond to the *f* impulses and eventually other motoneurons respond to the *i* impulses. The latency of the *f* wave (Fig. 4, *f*) is equal to the synaptic delay at the motoneurons, plus conduction time in the *f* fibers and in the motor nerve. The latency of the *i* wave includes in addition the synaptic delay at internuncial neurons. The appearance of the *i* wave depends on a number of conditions, among them being the state of

* The experiments reported in this paper were carried out at the Central Institute for the Deaf, St. Louis, Mo., and were aided by a grant from the Rockefeller Foundation.

the preparation, which determines the amount of tonic internuncial bombardment of the motor nucleus. Thus in the experiment illustrated by the records of Figs. 2 and 4, at the start the response contained only an *f* wave (Fig. 2, *7*, *8*), while later (Fig. 4, *3*, *6*, *13*) the *i* wave was almost as large as that of *f*.

The *f* wave, although of very short duration, is not a synchronous spike, which indicates the existence of slight differences in the delays at the individual motoneurons, there being a convincing reason to believe that the neurons with the longer synaptic delays are those stimulated at or only slightly above threshold. If the F shock is weakened (Fig. 2, *7*, *8*) the latency of the responses increases slightly or at least its crest appears later. The differences between the maximal and the minimal synaptic delays in submaximal responses, such as that in Fig. 2, *8*, is doubtless not greater than 0.2 msec., and consequently the longest synaptic delay in these responses may be calculated at 0.8–0.9 msec. This also may be regarded as the maximal synaptic delay at trochlear motoneurons, because the responses in record *8* include a number of motoneurons stimulated at threshold. However, this statement, although valid for the majority of the motoneurons in the nucleus, may not be applicable to all the motoneurons, because the action potentials of the smallest axons in the trochlear nerve scarcely would be detectable at the amplification used for obtaining the records shown in Fig. 2.

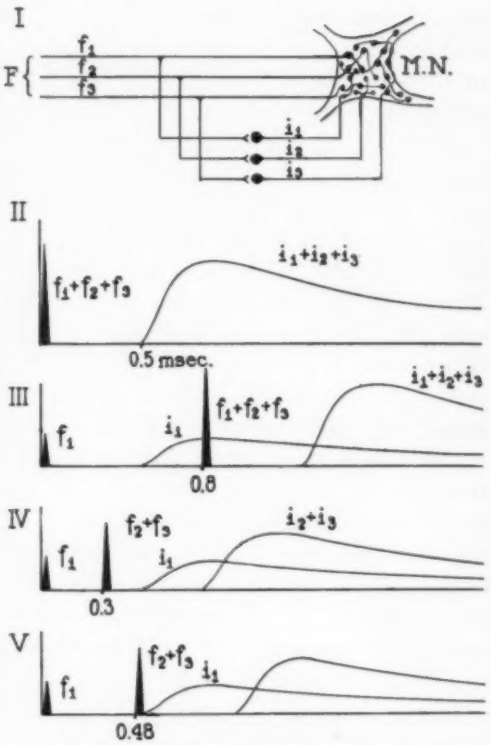


FIG. 1. Diagrams explaining the conditions of stimulation of the ocular motoneurons by delivery of shock through the F electrodes (cf. 1938b, Figs. 1 and 2).

I. f_1, f_2, f_3, fibers of the posterior longitudinal bundle; i_1, i_2, i_3, internuncial neurons, each cell actually representing a chain of neurons (1938b, Fig. 3). M.N., motoneuron with synaptic knobs.

II. A maximal shock capable of stimulating fibers f_1, f_2, and f_3 causes the arrival to the motor nucleus of an initial volley of impulses ($f_1+f_2+f_3$) followed by volleys of internuncial impulses ($i_1+i_2+i_3$). The ordinates indicate the number of impulses, the abscissae the time of arrival, measured from the start of their spike potentials.

III, IV, and V. The maximal shock is preceded at the intervals 0.8, 0.3 and 0.48 msec. by a smaller shock capable of stimulating fiber f_1 only. It is assumed that the refractory period of all *f* fibers is 0.52 msec. For the sake of simplicity it is assumed that the *i* volleys are not increased by facilitation.

A more conclusive proof of the existence of an upper limit for the dura-

tion of the synaptic delay is derived from the study of its lengthening during refractoriness (cf. Eccles, 1937) due to penetration of an antidromic impulse into the soma of the motoneurons. When a shock is delivered to the motor nerve at progressively decreasing intervals before the testing F shock (Fig. 3, *1* to *9*), the response is seen to decrease in size at the same time that its latency increases. However, the height drops much faster and the response disappears before the latency has increased by more than 0.2 msec. (cf. records *1* and *8* in Fig. 3). It is remarkable that the maximal value of the synaptic delay of the *f* response to weak stimuli is equal, as near as it can be measured, to the delay of responses to strong stimuli elicited during refractoriness.

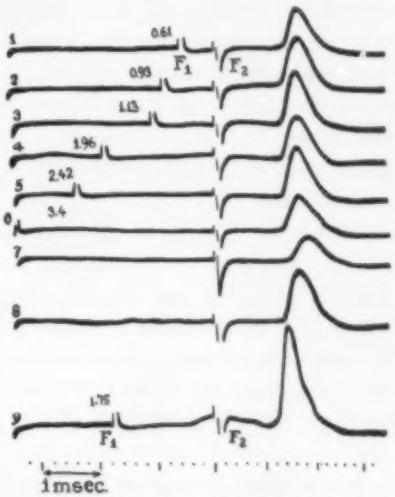


FIG. 2. Oculomotor preparation; responses recorded from the trochlear nerve (2-7-36). Testing shock (F2) 300 per cent stronger than the conditioning one (F1); for records *8* and *9* shock strength 30 per cent greater than for records *1* to *7*. The latencies to the responses to F2 in record *7*, and to F1 in record *9*, include the maximal synaptic delay; the latency to F2 in record *9* the minimal delay. The synaptic delay is calculated by subtracting from the total latency 0.7 msec., which is the conduction time of the impulses in fiber paths. Time in 0.2 and 1 msec. below. Interval between shocks indicated in msec. in records *1* to *6* and *9*.

This seems to establish a definite relationship of the synaptic delay, on the one hand, to the strength of the stimulus, and on the other hand, to the threshold of the motoneuron. Reduction of the strength of the stimulus, *i.e.*, decrease of the number of activated synapses, or the raising of the threshold of the motoneuron causes lengthening of the synaptic delay, and although the variation is small it may have theoretical significance.

However, it must be admitted that the experimental evidence is not entirely conclusive. The fact that refractory motoneurons respond demonstrates that when their threshold is normal, the synaptic stimulus is supermaximal, *i.e.*, that a number of synaptic knobs larger than the necessary minimum is activated. Since the *f* volley is not perfectly synchronous, the possibility exists that during refractoriness the initiation of the impulse takes place in a zone of the soma located under knobs receiving late *f* impulses or creating an excitatory process of longer duration than the shortest (cf. 1938a).

The synaptic delay of responses to shocks of about twice threshold strength cannot be shortened in an appreciable manner by further strengthening of the shock, even if it is accompanied by a substantial increase in the number of responding motoneurons. But facilitation due to previous stimulation may shorten the latency, although by not much more than 0.1 msec. This is well shown by records *8* and *9* of Fig. 2 and records *12* and *13* of Fig. 4. Records *1* to *7* of Fig. 2 demonstrate that during the period of facilitation the shorten-

ing of the delay is in direct relation to the increase in the height of the response.

An examination of diagram I of Fig. 1 yields the explanation. This diagram reveals that even maximal stimulation of the bundle of *f* fibers cannot result in maximal stimulation of the motoneurons, because there are many synaptic knobs which, belonging to *i* cells, cannot be activated unless those cells are made to fire. Obviously, the only possibility of maximal stimulation of motoneurons consists in delivering two F shocks in succession. The first F shock (cf. 1935c, 1938b) creates a certain amount of internuncial activity and thus the impulses of the *f* volley of the second F shock may summate with internuncial impulses (Fig. 1, III). If the internuncial bombardment is strong enough, some motoneurons will have all their synapses simultaneously activated and the stimulation will be maximal. In fact, in some cases the stimulation is so strong that it causes the motoneurons to fire impulses into their axons immediately after completion of the absolutely refractory period (1935b).

As the effect of facilitation and that of a rise in threshold are in opposite directions, they may compensate each other. For example, in Fig. 3, the latency of the response (record *10*) was shortened by facilitation (record *11*) so that it became a synchronous nerve spike; but refractoriness (record *12*) brought the latency back to its original value, or perhaps something less, because the speed of conduction in the motor axons may have been slightly subnormal.

On examining diagrams I and III of Fig. 1 it is realized that the shortening of the synaptic delay by facilitation involves a dual mechanism. On the one hand, facilitation increases the total number of impulses delivered to each motoneuron; and on the other hand, the *f* impulses of the testing shock arrive at the motoneurons some time after *i* impulses of the conditioning shock, so that the *f* impulses complete

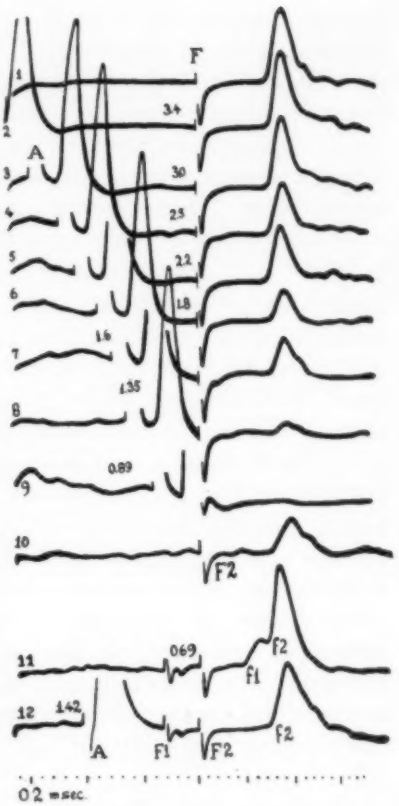


FIG. 3. Oculomotor preparation; responses recorded from the trochlear nerve.

Records *1* to *10* (2-2-36); a maximal antidromic shock (A) is delivered to the motor nerve at the intervals indicated in msec. before the testing F shock. The F response, shown unconditioned in record *1*, diminishes in height and appears after lengthened latency.

Records *10* to *12* (2-6-36); the response to a testing F2 shock (record *10*) is facilitated by delivery of a smaller F1 shock (record *11*), its latency also is decreased, but delivery of a maximal antidromic shock (A) 1.42 msec. before F1 obliterates the response to this shock and lengthens the latency of the response to F2 (record *12*). Time in 0.2 and 1 msec. below.

the stimulation initiated by the *i* impulses. That under such conditions the shortening of the delay is so slight is remarkable, and it must be related to the shortness of the period of effective summation of impulses arriving at neighboring synapses (1935d).

A direct examination of the problem has been carried out by the method of fractionation of the F volley (1935c), successfully applied by Eccles (1937) to the study of synaptic delays in the superior cervical ganglion.

In the experiment illustrated by the records of Fig. 4, two F shocks were delivered in succession. The conditioning shock (Fc) was slightly subthreshold and in diagrams III to V of Fig. 1 is supposed to have stimulated only fiber f_1; the testing shock was five times as strong and is supposed to have stimulated the whole bundle of F fibers. In constructing diagrams III, IV and V it also has been assumed that the absolutely refractory period of the *f* fibers measures 0.52 msec. (1935b).

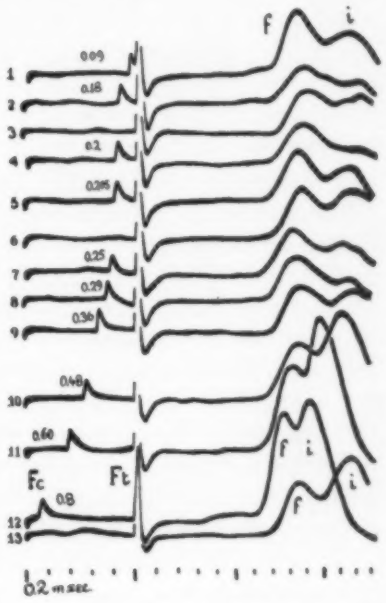


FIG. 4. Same experiment as in Fig. 2 but two hours later. Conditioning shock (F1) one-fifth of the testing shock (F2). Intervals between shocks indicated in msec. on the records. *3, 6, 13,* unconditioned responses to F2. Conditions of the experiment indicated in Fig. 1. *f,* response to the *f* impulses; *i,* response to the *i* impulses. Time in 0.2 and 1. msec. below.

Records *1* to *7* of Fig. 4 demonstrate that at intervals Fc–Ft of 0.25 msec. or less the latency of the response was reduced, the shortening being greatest but still less than 0.2 msec. at the interval of 0.2–0.25 msec. At 0.29 msec. (record *8*) the shortening was markedly less, and there was no shortening at the interval of 0.36 msec. (record *9*). Obviously, the period of summation of the f_1 and f_2+f_3 impulses was shorter than that interval.

Increase of the interval between shocks soon resulted in increase of the response. Facilitation was demonstrable at an interval of 0.48 msec. (record *10*); since at that time the f_1 fibers (Fig. 1, V) were still refractory, the increase of responses was due to summation of the f_2+f_3 impulses with i_1 impulses which arrived later. The latency, measured from the moment of delivery of the Ft shock, was of course not shortened. But at longer intervals (records *11* and *12;* cf. Fig. 1, III) the $f_1+f_2+f_3$ impulses were summating with i_1 impulses which had arrived previously, and the response not only was larger but also had a shortened latency.

It is important to note that the latency in records *7* and *12* is the same, a fact that was to be expected, because in both cases the response was due to the summated effect of impulses arriving in quick succession.

Comparison of the *f* waves of records *12* and *13* among themselves and with the time line shows the slight amount by which the delay of an impulse at one synapse may be reduced; but comparison of the *i* waves in those records reveals that if the impulse has to cross successively several facilitated neurons, the shortening may be considerable. In that case, where the impulses started by the Ft shock were obliged to cross first the *i* synapses and then the synapses on the motoneurons, the shortening amounted to about 0.4 msec.; but if they had to cross through three facilitated synapses the shortening would have been equal to a whole synaptic delay (0.6 msec.), and consequently the same as is obtained by "skipping" a synapse (1935c, Fig. 3, *20*, *21*).

Discussion

The delay of transmission of an impulse across synapses on the motoneurons varies between very narrow limits, the maximal variation being about 0.3 msec. In facilitated responses the delay measures 0.5–0.6 msec. and in threshold responses, 0.8–0.9 msec. However, it is possible that the limits of variation may be even smaller, because in the present measurements no correction has been introduced either for latencies of the *f* impulses at the F cathode, or for subnormal speed of conduction of the impulses in motor axons made refractory by the antidromic shock. With the present technique the amount of correction cannot be estimated, and therefore it is advisable to take the obtained figures as they stand and summarize the results in the following sentence. *A motoneuron stimulated by a volley of impulses delivered at its synapses either responds within 0.5–0.6 to 0.8–0.9 msec., or it does not respond unless restimulated by a new volley of impulses.*

The rigidity of the synaptic delay must be carefully taken into account in establishing the theory of synaptic transmission, for it is obvious that no excitatory process may be assumed which does not take place within that interval of time, as it is never finished in less than 0.5–0.6 msec. after arrival of the impulse or in more than 0.8–0.9 msec.

For descriptive purposes the synaptic delay is measured from the beginning of the arrival of the stimulating impulse at the synaptic knob, a procedure which masks the true time relations between stimulus and response. The stimulus, *i.e.*, the impulse delivered at the synapse, is not an event of vanishingly short duration; indeed, it has a duration which approaches and may even be as long as the synapse time itself.

According to Gasser and Grundfest (1936) the spike potential that accompanies the impulse along mammalian A fibers has a duration of about 0.5 msec. This must also be the duration of the spike in the *f* fibers, because judging by their threshold and refractory period these fibers belong to class A (1935a). Since the *f* fibers upon entering the motor nucleus branch out and diminish in caliber, it may be argued that their spike potential is lengthened, but at any rate no great lengthening may be assumed for the reason that a second effective impulse can be transmitted through synaptic terminals when started 0.52 msec. after the first (1935b) and it is believed that the ab-

solutely refractory period ends when the major part of the spike is finished (Adrian, 1921; Gasser and Grundfest, 1936). A new kind of response at the synaptic knobs can scarcely be admitted, because the knobs are not always found at the end of the fibers; in fact, they are often situated in the traject of long fibrils (1938a). Under conditions such as these it seems reasonable to assume that the major part of the spike, at least at some synaptic knobs known to be capable of setting up a response, lasts for about 0.5 msec. This, it will be noted, is the duration of the minimal synaptic delay, so that the conclusion becomes unavoidable that when these knobs are effective the stimulated neuron fires its own impulse at the moment when the spike potential at the knobs has subsided or finds itself at an advanced point of the descending phase. It may even fire 0.3 msec. later. Whether the latter is due to the fact that the spike potential at some knobs is of longer duration or that the volley of *f* impulses is slightly asynchronous, or is in fact due to a true delay in the setting up of the new impulse, cannot be decided at present. However, on the evidence available, especially the fact that the raising of the threshold lengthens the synaptic delay, it would not be unreasonable to assume that a true delay of that value may take place.

Emphasis must be laid upon the fact that the summation of impulses delivered in succession at neighboring synapses cannot reduce the synaptic delay below a minimal value, which is but slightly less than the delay observed after stimulation by a large synchronous volley of impulses. This indicates that the second impulse does not bring to completion the process started by the first; the second starts its own local process (cf. 1938a), which does not result in the setting up of the new impulse until the spike potential at its synaptic knob has subsided or is near completion.

Conclusions

1. The limits of variation of the synaptic delay of ocular motoneurons have been determined with an improved technique.

2. The average delay measures 0.7 msec. It may be shortened by facilitation or by increasing the number of activated synapses; and it may be lengthened by decreasing the stimulus or by raising the threshold of the motoneurons.

3. The minimal synaptic delay measures 0.5–0.6 msec., and the maximal delay 0.8–0.9 msec.

4. It may be calculated that the minimal synaptic delay is equal to the duration of the major part of the spike potential at the synaptic knobs.

5. Knowledge of the temporal course of synaptic transmission is not sufficient to identify the elementary process underlying transmission, but it reduces the number of possible assumptions. No process may be assumed that cannot take place within the now known rigid time constants.

REFERENCES

Adrian, E. D. The recovery process of excitable tissues. II. *J. Physiol.*, 1921, *55:* 193–225.

Eccles, J. C. Synaptic and neuro-muscular transmission. *Ergebn. Physiol.*, 1936, *38:* 339–444.

ECCLES, J. C. The discharge of impulses from ganglion cells. *J. Physiol.*, 1937, *91:* 1–22.

GASSER, H. S., and GRUNDFEST, H. Action and excitability in mammalian *A* fibers. *Amer. J. Physiol.*, 1936, *117:* 113–133.

LORENTE DE NÓ, R. The synaptic delay of motoneurons. *Amer. J. Physiol.*, 1935a, *111:* 272–282.

LORENTE DE NÓ. R. The refractory period of the motoneurons. *Amer. J. Physiol.*, 1935b, *111:* 283–288.

LORENTE DE NÓ, R. Facilitation of motoneurons. *Amer. J. Physiol.*, 1935c, *113:* 505–523.

LORENTE DE NÓ. R. The summation of impulses transmitted to the motoneurons through different synapses. *Amer. J. Physiol.*, 1935d, *113:* 524–528.

LORENTE DE NÓ, R. The electrical excitability of the motoneurons. *J. cell comp. Physiol.*, 1935e, *7:* 47–71.

LORENTE DE NÓ, R. Synaptic stimulation of motoneurons as a local process. *J. Neurophysiol.*, 1938a, *1:* 195–206.

LORENTE DE NÓ, R. Analysis of the activity of the chains of internuncial neurons. *J. Neurophysiol.*, 1938b, *1:* 207–244.

SYNAPTIC STIMULATION OF MOTONEURONS AS A LOCAL PROCESS

RAFAEL LORENTE DE NÓ
*From the Laboratories of The Rockefeller Institute for Medical Research, New York**

(Received March 21, 1938)

THREE lines of evidence justify the assumption that the initiation of an impulse by synaptic stimulation of a motoneuron is attributable to a process reaching threshold within a discrete zone of the soma, underneath a group of active synaptic knobs. (1) The soma of the motoneuron is electrically excitable and has a number of properties in common with peripheral nerve fibers. It must conduct propagated disturbances according to the all-or-nothing law, while subliminal disturbances must remain localized (1935d), *i.e.*, their spread away from the stimulated zone must be decremental, as is known to be the case in nerve (Hodgkin, 1937; Lorente de Nó, 1938a; cf. Eccles, 1936, 1937). (2) The period of effective summation of two volleys of impulses arriving in succession at different synapses is brief and summation does not essentially alter the time course of stimulation by the second volley (Lorente de Nó 1935b, c, 1938b, c; cf. Eccles, 1937). (3) Activation of a large number of synapses belonging to a certain set of pathways remains ineffective in the absence of bombardment of the motoneurons by impulses that have originated in internuncial pools of neurons (Lorente de Nó 1935c, p. 507; 1938c, Fig. 7, *13* to *20*).

The last line of evidence is doubtless the more direct one, and further experiments conducted on this basis have yielded results that seem to be unequivocal. These findings are presented here, together with anatomical data on the distribution of synaptic junctions on the soma of the motoneurons, which are necessary for an understanding of the facts observed.

TECHNIQUE

The experiments have been carried out on the oculomotor preparation of the rabbit, as previously described (1935a, 1938c). The anatomical studies have been conducted on the brainstem and spinal cord of young cats, and the specimens were stained with silver chromate after Golgi.

RESULTS

Experimental. During mild ether narcosis, not deep enough to modify the corneal reflex in an appreciable manner, but still sufficient to reduce or abolish the tonic labyrinthine innervation of the eye muscles, single F shocks are ineffective in setting up a synaptic response of ocular motoneurons, even when they are so strong that they must stimulate every fiber of the posterior

* The experiments reported in this paper were carried out at the Central Institute for the Deaf, St. Louis, Mo., and were aided by a grant from the Rockefeller Foundation.

longitudinal bundle and adjacent pathways. Under these conditions it cannot be doubted that a large number of synapses on the motoneurons are activated. In point of fact, in the absence of ether, large numbers of motoneurons, and eventually the total population of the motor pool, do respond. The absence of response during narcosis cannot be attributed, at least not wholly, to a direct effect of ether on the motoneurons, for the following reasons: (1) When two F shocks are delivered in succession at the proper interval, the second sets up responses that include large numbers of motoneurons (Figs. 1 and 2). (2) During ether narcosis shocks delivered to the nuclei of the reticular substance in front of the oculomotor nuclei set up synaptic responses of the motoneurons (1938d, Fig. 2). (3) Single F shocks are rendered ineffective if the vestibular nuclei and the reticular formation in the medulla are destroyed. (1935c.) (4) Single F shocks also remain ineffective if previous stimulation has temporarily suppressed the normally existent background of subliminal bombardment of the motor nucleus by internuncial impulses (1936, 1938c, Fig. 7).

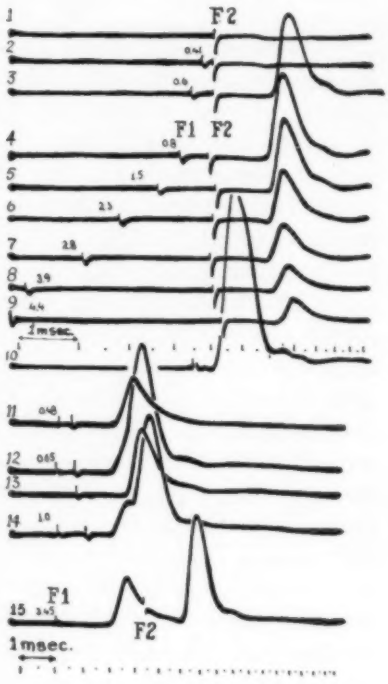


FIG. 1. Oculomotor preparation of the rabbit. Response recorded from the internal rectus muscle (6-11-36). Conditioning shock (P1) 50 per cent of the testing shock (F2). Intervals between shocks indicated in msec. on the records. Light ether narcosis for records *1* to *9*; no narcosis for *11* to *15*. *10*, maximal motor twitch.

In conditions such as these the conclusion is unavoidable that the activation of any number of *f* synapses in isolation is insufficient to stimulate the motoneurons to discharge impulses into their axons. A typical experiment is illustrated in Fig. 1. Two shocks in succession were delivered: F2 had twice the strength of F1; F1, in the absence of ether narcosis, was almost maximal for the F response to single shocks (Fig. 1, *11* and *15*). During ether narcosis both F1 and F2 delivered in isolation were ineffective (Fig. 1, *1*), but when F2 was preceded by F1, at intervals of 0.6 to 5 msec., it was followed by strong responses, which at certain intervals (Fig. 1, records *3* and *4*) had almost half the size of the maximal motor twitch (record *10*). A few minutes after discontinuing the narcosis, both F1 and F2 were individually able to set up strong responses (records *13* and *15*), and when delivered in succession at intervals of 0.6 to 5 msec., the F2 response also was facilitated.

The facts described below are significant. At intervals of 0.41 msec. (record 1) or 0.48 msec. (record *11*) the F2 shock was ineffective, either in setting up

any response at all, or in adding anything to the response produced by F1 (cf. records *11* and *15*). However, at 0.6 msec. (record *3*) or 0.65 msec. (record *12*), the F2 response was large, indicating that between the intervals of 0.41–0.48 to 0.6–0.65 msec. a change in the excitability of the motoneurons had taken place. Since in both records *3* and *12* the F2 response had the minimal synaptic delay, there is no doubt that in both cases the F2 response had been produced by *f* fibers not reached by the F1 shock, for the absolutely refractory period of *f* fibers is 0.52 msec. (1935b) and the impulses set up in refractory fibers by the F2 shock arrive at the motor nucleus after some delay and set up responses after lengthened latencies (1935b; cf. Fig. 2, *11*). The increase in excitability was so great that in the case of record *3* a limited number of *f* fibers set up a large response after the minimal synaptic delay (cf. 1938b, Fig. 1), while in record *1*, a more powerful volley of *f* impulses was unable to fire any motoneuron. On the other hand, as the response in record *3* was caused by fibers not stimulated by F1, the change in excitability cannot be ascribed to repetitive stimulation of synapses.* Under conditions such as these the only plausible assumption is that internuncial neurons responded to the impulses set up by the F1 shock (cf. 1938b, Fig. 1), and that these internuncial impulses when added to the *f2* impulses were capable of stimulating the motoneurons to discharge. Therefore, it must be concluded that the *f1* impulses, although they were unable to fire motoneurons, could fire internuncials; and that the internuncial impulses alone were incapable of firing motoneurons.

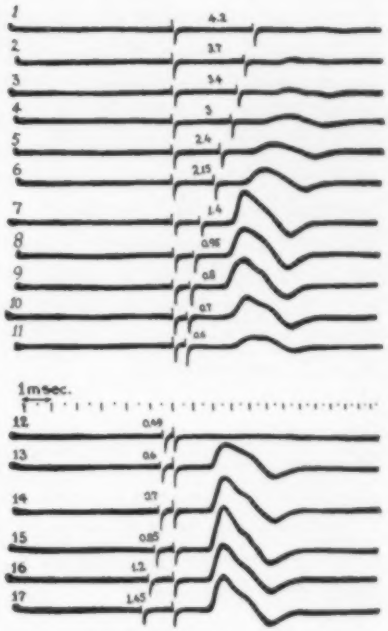


FIG. 2. Oculomotor preparation. Responses recorded from the internal rectus muscle (6-4-36). Light ether narcosis throughout. Intervals between shocks indicated in msec. on the records. The larger shock was maintained at a fixed position at the center of the oscillograph, while the smaller shock, 50 per cent of the larger one, was progressively displaced.

The same facts are presented in a more striking manner by the records shown in Fig. 2, which belong to another experiment. For the series of records *12* to *17*, since F2 had twice the strength of F1, the same conditions were created as were present in the case of Fig. 1, *1* to *9*, and identical results were obtained. It will be noted that the response at the start of the period of facilitation (record *13*) had the minimal synaptic delay, and consequently was caused by impulses conducted by the fibers not reached by F1.

* In the absence of ether narcosis, when the excitability of internuncial neurons is high, facilitation has been observed to begin 0.43–0.48 msec. after delivery of F1, *i.e.*, at a moment when all the fibers stimulated by F1 were still absolutely refractory (1935c, 1938d).

In the case of records *1* to *11*, the F2 shock preceded the smaller F1, so that repetitive stimulation of *f* fibers was necessary to produce the response. It will be seen that at the 1.4 msec. interval, when it was expected that a large number of *f* fibers had recovered the response (record *7*) was practically identical with that shown in record *17*. But at shorter intervals the responses in series *11* to *8* were consistently smaller than those at the same intervals in series *13* to *16*. They were also delayed, which indicates that the *f* impulses had been conducted to the motor nucleus with subnormal speed. As a matter of fact, the series of records *11* to *7* is like that regularly obtained with the nerve-muscle preparation after delivery of two shocks at similar intervals. This result can be graphically expressed in a simple manner. The internuncial discharge started by the conditioning shock created a subliminal stimulation of the motoneurons, so that the motoneurons responded to every *f* impulse that they received, with the result that the number of responding motoneurons became proportional to the number of recovered *f* fibers. Thus we have the following facts: (1) in record *1* a maximal *f* volley was unable to set up a response, while in records *13* and *11* small *f* volleys did produce responses; (2) in records *11* to *8* the numbers of responding motoneurons were roughly proportional to the numbers of the *f* impulses. The conclusion lies at hand that the strength of stimulation of motoneurons depends not only on the number of simultaneously activated synapses, but also on other conditions, one of which must be the topographical distribution of the synapses over the soma of the motoneuron.

Anatomical. It is at present generally recognized that the synapses on the motoneurons are formed by small thickenings of nerve fibers, located on the body and dendrites.*

The synaptic thickenings have been designated in the literature by various terms, which as a rule include the adjective "terminal" and often the noun "feet," for instance, the end or terminal feet of Held. Recently the designation, *boutons terminaux*, used in the French translation of Cajal's book (1909) has been widely employed. Given the extreme variety of forms of the thickenings of the axon (cf. Cajal, 1935), any term already used to designate another object is obviously improper, but this impropriety is unavoidable in the present case. Here the term "knob," suggested by Auerbach, is used. The adjective "terminal" also is improper, and even more, it is misleading; here use is made of the noncommittal designation "synaptic."

The distribution of the synaptic knobs on the motoneurons and other multipolar neurons has in the past been studied in stains made with reduced silver according to the methods of Cajal, Bielschowsky, or their modifications which, however, yield only incomplete pictures and as a rule give the impression that each knob forms the ending of a fibril. It is exceptional to obtain pictures which demonstrate the fact that several knobs belong to a single fibril. But even in the best anatomical picture ever published (Cajal, 1909, Fig. 436), the distribution of all the knobs belonging to each of the fibrils cannot be observed. Ordinarily, the silver picture is incomplete on another count; it fails to show many of the knobs present on a cell, and even all the knobs on by far the largest number of cells in the gray matter. For example, many of the knobs reproduced in Figs. 3 and 4,

* In some cells, such as the Purkinje cells of the cerebellum, the synapses extend to the initial segment of the process called axon. The same seems to be true for some types of internuncials in the spinal cord. As the axon often starts from dendrites at considerable distances from the body of the cell, it is a matter of definition whether to place the origin of the axon at the cell body and to consider that its initial part may carry synapses, or to hold that the axon starts at the level of ending of the synaptic scale of the cell.

in point of fact all those establishing synaptic junctions on dendritic branches, are not stained or cannot be identified with the use of the ordinary silver stains.

The silver staining methods are, of course, capable of improvement, and the yield obtained is in relation to the experience and knowledge of the worker using them. No theoretical reason exists why it should be impossible eventually to stain any synaptic junction with reduced silver. But in the experience of the present author, the silver chromate method of Golgi is the only one known to be capable of staining simultaneously and completely the synaptic knobs and the fibers to which they belong. Satisfactory stains can be obtained of sections from the spinal cord of cats even 20 days old (older animals have not been used), and sections of the hypoglossus, facial and oculomotor nuclei of 30 day old cats have been so stained. As a rule, the synaptic knobs in the cord can be studied in the 10–15 day old cat. It is a rather general belief that the knobs develop late, but the fact underlying this belief is that reduced silver methods fail to yield satisfactory stains at those ages. However, when synaptic junctions from animals at ages at which completed myelinization begins to prevent obtaining a satisfactory Golgi stain are compared with synaptic junctions from young but fully developed or even adult animals, stained with the Golgi-Cox method, no essential difference is observed.

Cells *A* to *E* in Fig. 3 are motoneurons and cell *I* presumably is large internuncial. All of these cells are from the anterior horn of the lumbar cord of a 15–16 day old cat. In the original preparation they are stained a light orange color, while the fibers and knobs are stained black or a deep red. The number of stained fibers is small, and hence there is opportunity to follow each fiber and its branches throughout their entire traject within the 100μ thick section.

From the majority of fibers near the group of motoneurons *A* to *E* only relatively short segments are included in the section; but there is a fiber *6* which has a relatively large segment and is seen to establish synaptic junctions with two motoneurons, *B* and *C*. Fiber *6* which also establishes synaptic junctions with dendrites is a branch of a slightly thicker fiber, which in turn is a collateral of another fiber of the anterolateral tract. The parent fiber, therefore, establishes connections with many motoneurons and internuncials —a well-known fact which does not require emphasis.

It will be noted that during its traject along cell *C*, fiber *6* gives off a series of branches, each one of which ends on cell *C* by means of one, two, or even a cluster of knobs. The total number of knobs is large, but it is remarkable that these knobs are not located in the immediate proximity of one another, being separated by spaces which are no doubt occupied by knobs belonging to other fibers. Fiber *6* then divides into two branches, *6 a* and *6 b*. Fiber *6 a* has five knobs on the body of cell *B* and finally ends in an intercellular space having several small synaptic thickenings (*d*) obviously in contact with dendrites. Fiber *6 b* establishes contacts presumably only with dendrites.

The connections of fiber *2* with cell *C* also are clearly seen in the preparation. Branch *2 a* obviously establishes contacts only with dendrites, for no cell body can be located in that narrow intercellular space; but branch *2 b*, after having formed some knobs *d* in contact with dendrites, has a traject parallel to the border of cell body *C*, in the course of which it gives off tiny branches terminated by knobs on cell body *C*. It will be observed that the second fibril before reaching *C* has two tiny thickenings which must necessarily be in contact with dendrites.

Another type of fiber having contacts with cell *C* is fiber *5*, which ends with a cluster of knobs at the base of a large dendrite. In the case of cell *C* the orientation of the section is such that fibers *2* and *6* happen to be in the equa-

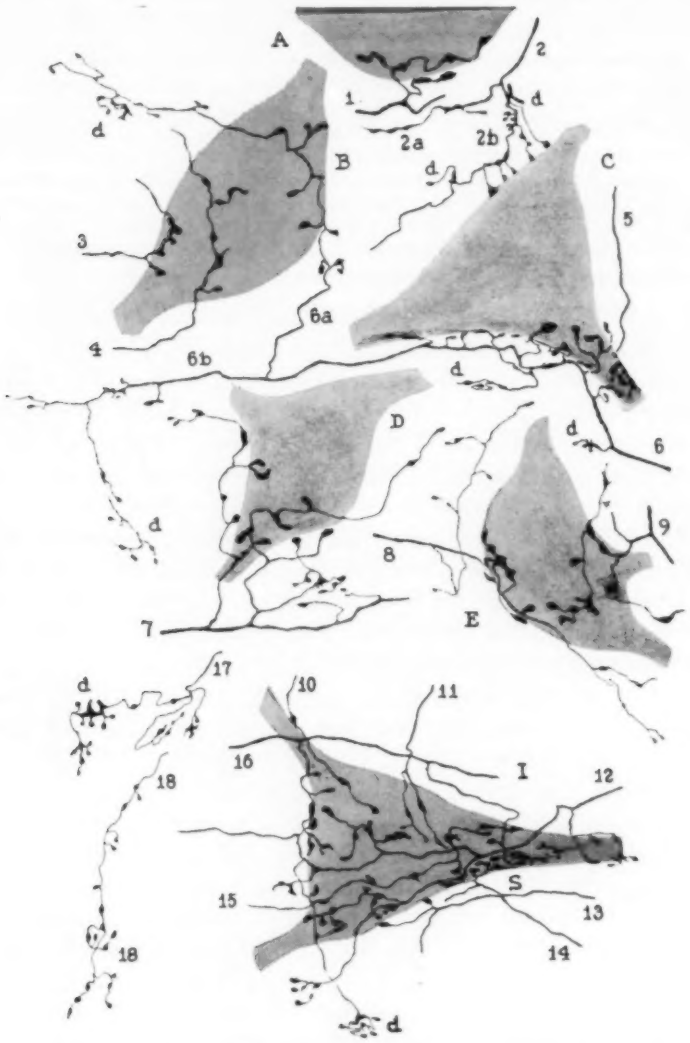


FIG. 3. Synapses on motoneurons (A to E) and on a large internuncial (I) of the spinal cord of a 15–16 day old cat. Silver-chromate method of Golgi. *d*, synaptic knobs in contact with dendrites.

torial plane of the cell body, so that the true relations of cell, fibers, and knobs can be observed. This relationship can still be seen, although but partially, in the case of fiber *7* and cell *D*. The knobs are in contact with the cell body,

but the fibrils connecting the knobs are not in contact with the cell. In the spaces left by the connecting fibrils and the cell, other fibers and tiny dendritic branches are located. In the case of cells *A*, *B*, and *E*, the stained synapses are located on the upper surface of the cell and for this reason the distances between the knobs formed by each fiber are better observed than in the other cells.

All these pictures are, of course, incomplete because only a few fibers were stained. The body of the cell is in fact always entirely covered with synaptic knobs belonging to many fibers, which form a continuous synaptic scale. It is obvious from the drawings of Fig. 3 that the synaptic scale is a mosaic of interlacing clusters of knobs, so that the activation of any discrete zone of the synaptic scale demands the conduction of impulses by several fibers. On the other hand, one fiber may help activate several different zones of the synaptic scale. An attempt to illustrate these facts in graphic form is made in the drawing of cell *I* taken from another section, and seven (*10* to *16*) of the stained fibers having knobs on the upper surface of the cell. It will be noted that while fibers *10*, *11*, *13* and *14* have but a small number of knobs, fibers *15* and especially *12* and *16* have numerous knobs distributed over a wide area of the cell body. The motoneurons and large internuncials receive knobs from so many fibers that a complete picture is obtained only when the preparation is so heavily stained that the course of the individual fibers cannot be investigated in detail; but the small internuncials, especially in Cajal's intermediate nucleus, receive knobs from a relatively small number of fibrils, and therefore not infrequently one observes pictures such as that shown in Fig. 4, in which an important part of the synaptic scale is stained, while the cell itself has remained unstained.

FIG. 4. *A*, synapses on a small internuncial neuron of the ventral ganglion of the acoustic nerve of a 20 day old cat. *B*, a cell of the same type. *a*, axon; *b*, *c*, *d*, d_1, dendrites: f_1 to f_6, fibers having synaptic junctions with cell A.

Ten fibers (f_1 to f_{10}) having synaptic junctions with the upper surface of the cell body or dendrite *d*, or both, have been reproduced in the drawing. It can be seen that fibers f_7 to f_{10} join dendrite *d* at some distance from the cell body, presumably at its point of bifurcation; the fibers follow the den-

drite, having small thickenings in contact with it, and upon reaching the body form synaptic knobs in a manner similar to the fibers represented in Fig. 3. Fibers f_2, f_3, and f_4 reach the cell at the origin of dendrite *b*, and fibers f_5 and f_6 at the origin of dendrite *c;* a collateral of fiber f_1 reaches the cell body at a point which has no dendrite. It is obvious that if only a few more fibers had been stained, the synaptic scale would have been complete. Presumably it is almost complete at the level of dendrite *d*. While neighboring synaptic knobs are near each other, the distances being measured in fractions of μ, they are still not in actual contact. Between them there seems to exist an amorphous substance, which by Golgi's method is at times stained a brownish red color. The nature of this substance is unknown; at present it cannot even be said whether or not it differs from the intercellular fluid. Neither can it be determined definitely whether it corresponds to the pericellular network described by Cajal, Golgi and others (cf. Cajal, 1935, Fig. 47). We can only state with certainty that between the synaptic knobs there is something which takes the Golgi stain in a manner different from the knobs themselves.

The drawing of Fig. 4 also illustrates another important fact. The continuous synaptic scale formed by interlacing clusters of knobs extends over the dendrites, but for only a short distance, usually up to the point where the dendrites branch out, and sometimes even for a shorter distance. This, with but few exceptions, is the general rule for all the types of neurons studied by the present author in the spinal cord, medulla, midbrain, thalamus, and cerebral cortex. The differences observed refer chiefly to the extension of the synaptic scale beyond the limits of the cell body, the size of the knobs, the homogeneity of the fibers contributing to the scale, etc.

For the synaptic junctions of dendrites the description must be made in general terms, for the reason that a detailed analysis has not yet been completed. On the other hand, not all dendrites are alike, and there are important differences between dendrites of cells of various types, and even between the dendrites of one cell.

A general description may be attempted in the following terms. In the intercellular spaces, *i.e.*, in the spaces between cell bodies, there are besides glia cells, blood vessels, and myelinated fibers, two plexuses—one formed by dendritic branches, and the other by unmyelinated fibers which carry numerous synaptic thickenings. Fibers *17* and *18* of Fig. 3 are typical fibers of the plexus in the anterior horn of the cord, and so are the thin collateral branches of the other fibers in the same figure. Accurate representations of the dendritic plexuses have been given in other publications (cf. 1938c, Fig. 1; 1933, Fig. 12). Both dendritic and fibrillar plexuses have numerous synaptic junctions. It can be said that a dendrite while crossing the fibrillar plexus establishes junctions with fibrils of most varied origin, and that a fibril while crossing the dendritic plexus makes junctions with numerous dendrites of various types of cells. An attempt to illustrate graphically the relation between the two plexuses is made in the diagram of Fig. 5.

In parts of the nervous system where the arrangement of the dendritic

and fibrillar plexuses is systematic, as for example in the cerebral cortex and the tuberculum acusticum, it is possible to establish the existence of an orderly regional arrangement of synapses on the various dendrites (1933, 1934); but in the anterior horn of the spinal cord and the motor nuclei of the cranial nerves, an analysis of the dendritic connections is made difficult by the apparent lack of regularity.

There are motoneurons with dendrites distributed exclusively within the limits of the motor pool, and consequently the dendrites have connections with fibers also contributing to the synaptic scale on the cell bodies. But other motoneurons have dendrites extending far beyond the limits of the motor pool, and these have connections with the fibrillar plexus of internuncial pools. There are internuncial cells located in the immediate proximity of the motor pool, with no dendrite penetrating the latter; but there are also internuncial cells, sometimes with the bodies at considerable distances from the motor pool, which send dendrites into the pool, where they establish contacts with the fibrillar plexus of the latter. It is obvious that for the dendrites the same general rule holds as for the cell bodies, namely that activation of all the synapses in any discrete length of a dendrite demands the simultaneous conduction of impulses by several fibers of the plexus.

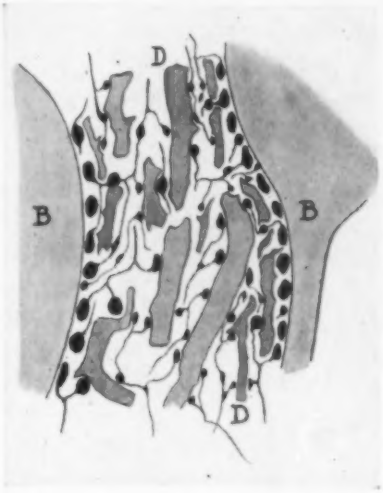


FIG. 5. Diagrammatic representation of the articulation of the dendritic and fibrillar plexuses in the gray matter of the spinal cord. Cell bodies (*B*) and dendrites (*D*) in gray; fibrils and synaptic knobs in black.

DISCUSSION

Threshold stimulation of a motoneuron does not require the activation of all the synaptic knobs, for the stimulation may have all gradations of intensity, from subliminal to supramaximal, *i.e.*, capable of firing a refractory neuron. On the other hand, the stimulation may be produced by the activation of different sets of knobs. This conclusion may be reached from a study of the experiments shown in Figs. 1 and 2, but more direct proof has been obtained in experiments in which it was shown that the same motoneurons may respond either to an *f* volley or to one of internuncial impulses (1938c, Figs. 3, 4 and 5). Increase in the number of knobs active constitutes an increase in the strength of stimulation; but the number of active knobs is not the only determining factor, because it has been shown that a small volley of *f* impulses may set up a response, while a large *f* volley may fail to do so. In view of the anatomical data, the most reasonable explanation seems to be that stimulation of the motoneuron demands the activation of all the synapses

on a discrete zone of the motoneuron, a condition that in the present experiments cannot be fulfilled by the activation of *f* or *i* fibers alone, undoubtedly because the synapses of each kind are scattered over the neuron. For example, let it be assumed that in Fig. 3, *I*, fibers *10*, *11*, *12*, *13*, *15* and *16* are *f* fibres. Stimulation of any number of these fibers will fail to activate all the synapses or any discrete zone of the soma; but if to the *f* volley an impulse through fiber *14* be added, all the synapses on the zone marked with *s* will be activated and the neuron will fire. Obviously, if fiber *14* conducts an impulse, there is no need for all the other fibers to be activated; threshold stimulation will be obtained if fibers *12* and *16* only are active. Obviously, other sets of fibers will cause the impulse to start at another zone of the soma.

This explanation, which is supported also by the first two lines of evidence mentioned in the introduction, applies as well in the case where the effective knobs are located on the cell body as in that of knobs located on dendritic branches. The latter, for example, is true of the olfactory bulb, because the olfactory fibers establish synapses with the dendritic bushels of the mitral cells. However, much work must still be done before the role of the various types of dendrites is fully understood.

The fact that liminal stimulation is obtained by the activation of a discrete zone of the soma does not indicate that the subliminal disturbance produced underneath any knob does not spread for a certain distance. The fact that summation takes place demonstrates conclusively that it does spread, at least to the next knob (Eccles and Sherrington, 1931). But the available evidence does not provide us with sufficient data to estimate the amount of the spread. The only permissible assumption is that effective summation demands the activation of knobs located at a distance from each other which is shorter than in the case of knobs belonging to one fiber.

An interesting conclusion to be drawn from this discussion is that the *f* and *i* synapses, which during ether narcosis are activated by shocks delivered to the posterior longitudinal bundle, are scattered over the soma of the motoneuron, so that an *f* or an *i* volley in isolation cannot result in the activation of all the synapses on any discrete zone of the motoneurons, but the *f* synapses must be so concentrated on some *i* cells that an *f* volley fires them. This conclusion is in agreement with known facts.

From the anatomy of the oculomotor preparation (cf. 1938c, Figs. 1 and 2) it follows that the *F* shock activates the posterior longitudinal bundle and adjacent pathways, which after giving collaterals in the oculomotor nuclei, end in the internuncial nuclei containing chiefly small neurons. The synaptic scales on these neurons are of the type illustrated in Fig. 4 and may be activated, at least in large zones, by the volley of *f* impulses. Thus it could be assumed beforehand that these neurons would respond to any *f* volley which is sufficiently large. Similarly, it could have been predicted that a volley of impulses conducted by the axons of these cells would in isolation be insufficient to fire motoneurons, for as these axons are thin, they can have but few contacts with any neuron. Neither is there difficulty in explaining why under

ether narcosis facilitation is of short duration. The large neurons of the internuncial nuclei having synaptic scales of heterogeneous origin are not activated by the *f* impulses. Therefore, long closed chains of neurons do not come into play, and facilitation ceases as soon as the impulses have crossed all the synapses in the open delay paths, which in the case of the experiments recorded in Figs. 1 and 2 means four or five internuncial synapses. But what was rather astonishing was to find the *f* volley in isolation incapable of firing motoneurons, for the powerful branches of the posterior longitudinal bundle form extensive arborizations in the motor nucleus. Attempts to analyze the distribution of the *f* synapses in the oculomotor nucleus have as yet failed, for the anatomical conditions present are unfavorable for detailed study. But in the hypoglossus nucleus it has in fact been found that each one of the long bundles sending collaterals into this nucleus has a certain type of terminal fibers in the nucleus, and that the axons of the small internuncials located in the neighborhood of the motor pool again have their specific distributions. It is, therefore, likely that the *f* synapses on the ocular motoneurons are systematically arranged on strategic zones of the neurons, so that only the summation of *f* impulses with impulses carried by other pathways is possible. It will be remembered that if a shock is delivered to the internuncial nuclei in front of the oculomotor nucleus, so that *f* and *i* fibers are stimulated simultaneously, ether narcosis does not prevent some motoneurons from responding; and that if a background of internuncial activity is present, the *f* volley may fire the entire population of the motor pool.

Summary

Although the threshold stimulation of motoneurons requires that several impulses be delivered simultaneously at their synapses, not all the fibers contributing to the synaptic scale need be active. Experimental results demonstrate that while the activation of a large number of synapses may remain ineffective, activation of a limited number of those synapses, effected simultaneously with the stimulation of other fibers, results in the setting up of a response. Furthermore, it is shown that effective stimulation of motoneurons may be produced by the activation of different groups of fibers.

Anatomical studies have revealed that the synaptic scale of the motoneurons consists of interlacing clusters of knobs belonging to a large number of fibers and that the synaptic terminals of each fiber are located at some distance from one another. The activation of all the synaptic knobs at any discrete zone of the soma demands that several fibers be conducting impulses. It is obvious that different groups of fibers will cause stimulation at different zones of the soma.

It is concluded, therefore, that the setting up of a new impulse by the motoneuron results from a localized process taking place underneath a dense group of active synaptic knobs. Subliminal responses must be propagated decrementally but the information available is insufficient to estimate the amount and rate of the spread.

REFERENCES

CAJAL, S. R. *Histologie du système nerveux de l'homme et des vertébrés.* Paris, Maloine, Vol. I. 1909.

CAJAL, S. R. Die Neuronenlehre. In BUMKE and FOERSTER, *Handbuch der Neurologie,* 1935, *1:* 887–994.

ECCLES, J. C. Synaptic and neuro-muscular transmission. *Ergebn. Physiol.,* 1936, *38:* 339–444.

ECCLES, J. C. The discharge of impulses from ganglion cells. *J. Physiol.,* 1937, *91:* 1–22.

ECCLES, J. C., and SHERRINGTON, C. S. Studies on the flexor reflex. V. General conclusions. *Proc. roy. Soc.,* 1931, *B107:* 597–605.

HODGKIN, A. L. Evidence for electrical transmission in nerve. I. *J. Physiol.,* 1937, *90:* 183–210.

HODGKIN, A. L. Evidence for electrical transmission in nerve. II. *J. Physiol.,* 1937, *90:* 211–232.

LORENTE DE NÓ, R. Anatomy of the eighth nerve. III. General plan of structure of the primary cochlear nuclei. *Laryngoscope., St. Louis,* 1933, *43:* 327–350.

LORENTE DE NÓ, R. Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system. *J. Psychol. Neurol., Lpz.,* 1934, *46:* 113–177.

LORENTE DE NÓ, R. The synaptic delay of motoneurons. *Amer. J. Physiol.,* 1935a, *111:* 272–282.

LORENTE DE NÓ, R. The refractory period of the motoneurons. *Amer. J. Physiol.,* 1935b, *111:* 283–288.

LORENTE DE NÓ, R. Facilitation of motoneurons. *Amer. J. Physiol.,* 1935c, *113:* 505–523.

LORENTE DE NÓ, R. The electrical excitability of the motoneurons. *J. cell comp. Physiol.,* 1935d, *7:* 47–71.

LORENTE DE NÓ, R. Inhibition of motoneurons. In *The problems of nervous physiology and of behaviour.* Jubileum Symposium, dedicated to Prof. J. S. Beritoff. Tiflis, Georgia Branch Acad. Sci. U.S.S.R., 1936, pp. 231–247.

LORENTE DE NÓ, R. Subliminal stimulation of medullated frog nerve. *Amer. J. Physiol.,* 1938a. (in press).

LORENTE DE NÓ, R. Limits of variation of the synaptic delay. *J. Neurophysiol.,* 1938b, *1:* 187–194.

LORENTE DE NÓ, R. Analysis of the activity of the chains of internuncial neurons. *J. Neurophysiol.,* 1938c, *1:* 207–244.

LORENTE DE NÓ, R. Responses of motoneurons and of motor axons to short induction shocks. 1938d, *J. Neurophysiol.* (To be published)

ANALYSIS OF THE ACTIVITY OF THE CHAINS OF INTERNUNCIAL NEURONS

RAFAEL LORENTE DE NÓ
From the Laboratories of The Rockefeller Institute for Medical Research, New York

(Received March 21, 1938)

INTRODUCTION

ALL THE neurons in the central nervous system are reciprocally connected by numerous pathways, some having great and others lesser degrees of complexity. This wealth of connections is due not only to the high number of neurons and pathways, but also to the branching of the axons and their collaterals and to the overlapping of the fields of distribution of the branches of the different axons. The number and complexity of central pathways are best described by saying that, with but few exceptions, at least one pathway can be found connecting any two central neurons in a manner so that an impulse may be conducted from one to the other neuron in the direction of axon-synapse-body or dendrite-axon. Obviously many of these complicated paths are physiologically impassable, because the impulses sooner or later fail to reach the threshold of an intervening neuron, but others actually do play an important role in the physiology of the central nervous system. This question was discussed at some length in previous papers (1928, 1933c, 1934a) in which the literature of the subject has been reviewed. Recent advances in the knowledge of the physiology of the synapse (reviewed by Eccles, 1936b, 1937a, b; Bremer and Kleyntjens, 1937; Fulton, 1938; Lorente de Nó, 1938b, c) make it possible to analyze in greater detail the physiological significance of the arrangement of the neurons in synaptic chains.

The interest of the analysis consists in that it is possible to reduce the actual anatomical complexity of the nerve centers to simple diagrams suitable for theoretical arguments. Within the extreme variety of connections established by any one neuron with neurons of the same or of distant pools there is a systematic repetition of two fundamental types of circuit, which may be called the multiple (Fig. 2, *M*) and the closed chain of neurons (Fig. 2, *C*). The chains may be longer or shorter, they may contain a larger or smaller number of parallel branches, but in every case they remain essentially the same. Thus it comes about that the cerebellum as an organ is, from the point of view of elementary physiology, a giant chain of internuncial neurons, superimposed upon the reflex arcs in the spinal cord and the medulla (1924). Its activity consists in regulating the transmission of impulses through the shorter arcs. Similarly, the complex anatomical mechanisms found in the reticular substance of the medulla, pons, and midbrain can be reduced to chains superimposed upon the shorter arcs, and it is understandable that if the short arcs have been destroyed through suitable operation, motor reactions can be elicited through the longer chains of the reticular formation (1928; Spiegel,

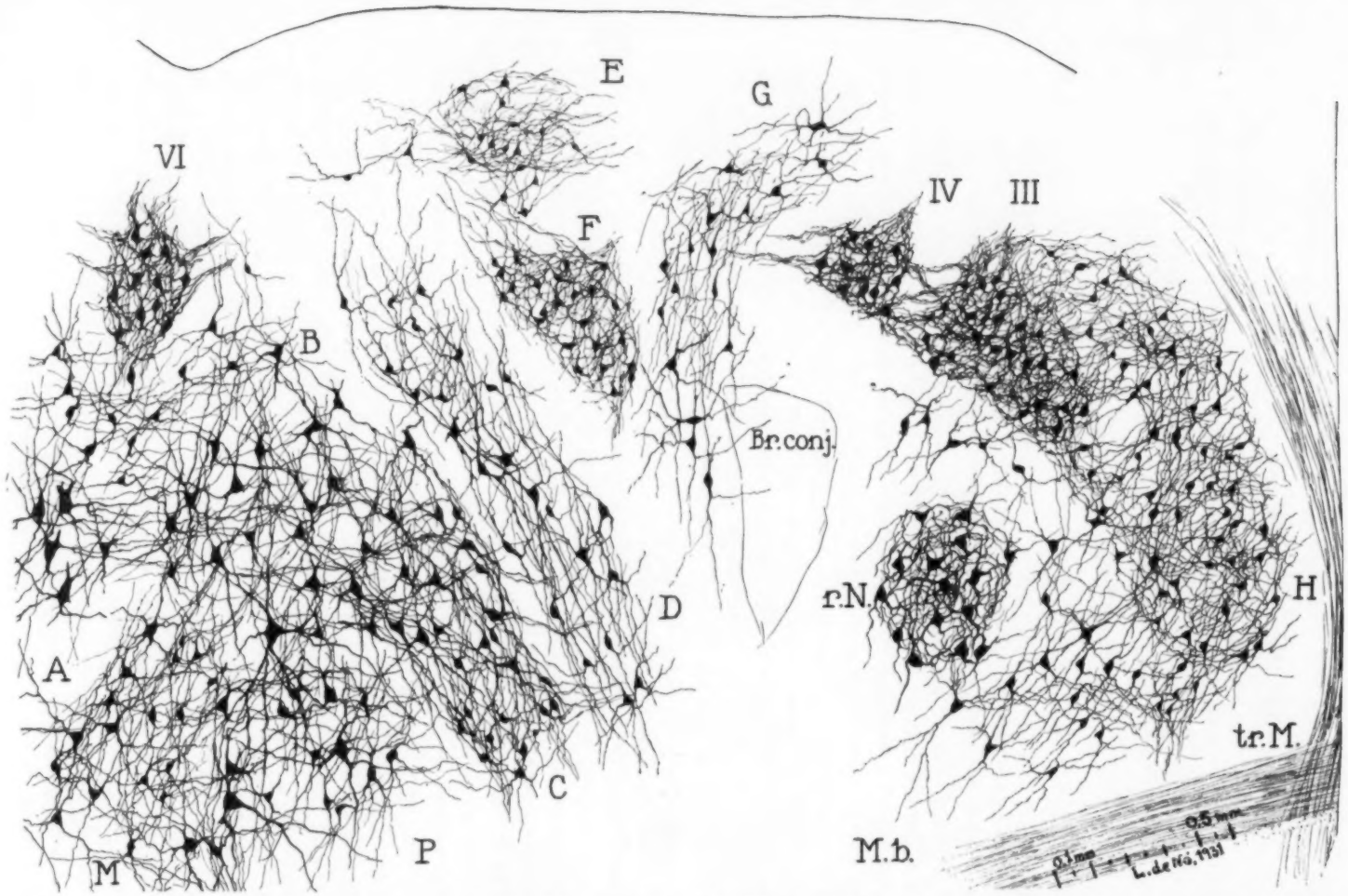


FIG. 1. Longitudinal section through the medulla (M), pons (P), and midbrain (M.B.) of an adult mouse. Golgi-Cox stain. Drawing made with help of the projection apparatus from a single 80μ thick section. III, IV and VI, the oculomotor nuclei; *r.N.*, red nucleus; *Br. conj.*, crossing of the superior cerebellar peduncles. A, B, C, D, E, F, G, and H nuclei of the reticular substance. A, B, C, D and H belong to the motor correlation system and have connections with the oculomotor neurons. E, F, and G belong to the autonomic system. *tr.M.*, tract of Meynert.

1929). Nor is it difficult to account for the fact that the internuncial system in the reticular formation may be the locus where inhibition of motor responses is produced (1928, 1931; cf. Sherrington, 1934).

An analysis of the activity of the chains of internuncial neurons has been made in the oculomotor preparation (1935a) which affords an opportunity of stimulating large fiber tracts known to establish synaptic connections with the ocular motoneurons. Diagrammatic representations of the preparation have been given in previous reports (1935a, e) but additional details are needed.

Since in physiological literature the internuncial system has not received the attention that its anatomical importance justifies, it is necessary first to reproduce an actual anatomical picture in which the relative number of motor and internuncial neurons is immediately seen. Fig. 1 reproduces part of a section through the medulla and midbrain of an adult mouse stained after Golgi-Cox. It contains the oculomotor nuclei (VI, IV, and III) and a few of the nuclei of the system of correlation located in the reticular formation of pons and midbrain. In it, it is patent that the motoneurons are outnumbered many times by the internuncial cells* of the reticular formation, which regulate their discharge.

Actual reproductions of pathways connecting these neurons among themselves and with the motoneurons have been published by a number of authors (Cajal, 1909, Fig. 361; 1911, Figs. 151, 155, 156, 157; Whitaker and Alexander, 1932; Lorente de Nó, 1924, 1933a, c, e, etc.). The diagram in Fig. 2 has been constructed on the basis of these data.

The diagram emphasizes several important points: (1) Next to pathways (1, 2, 9, 10, 11) having direct connections with the motoneurons there are pathways (3, 4, 5, 7, 8, 12) that end in the reticular formation without direct connections with the motoneurons. Therefore the impulses which they carry can reach the motoneurons only after having crossed through an additional internuncial neuron. (2) All the pathways that establish connection with the motoneurons also have synapses with cells of the reticular formation, so that

---

* The name internuncial neuron is ambiguous, because every neuron in the central nervous system, with the exception of the motoneurons, may be called internuncial. But the classification of the cells in each particular case is not difficult if the following argument is considered. Impulses are conducted into a pool of neurons by afferent fibers and out of the pool by efferent fibers, which are axons of some cells of the pool. The cells of origin of the efferent fibers transmit the effect of the activity of the pool and may be called "effector neurons"; all the other nerve cells in the pool are internuncial neurons. Consequently a cell may be called effector or internuncial according to the problem being studied. In the present case the axons of cells in the vestibular and reticular nuclei that run directly to the motor nucleus and are stimulated by the shock are not called internuncials because they are made to play the role of afferent fibers; but if the shocks were delivered to the vestibular nerve, all the cells in the reticular nuclei would be internuncials of the second, third, etc. order, according to the number of synapses crossed by the vestibular impulses on their way to the motor nucleus.

The concept of the internuncial cells is radically different from the concept of the intercalar cell (Schaltzellen of v. Monakow) because, as Cajal long ago (1911, p. 590) pointed out, the cells with short axis cylinders to which v. Monakow referred are not intercalated between the afferent fibers and the cells with long axis cylinder; they form a collateral chain superimposed upon the articulation of afferent fiber-cell with long axon.

whenever an impulse is delivered to a motoneuron, impulses also arrive at internuncial cells. (3) The internuncial neurons are arranged in chains of two types: *M* (principle of plurality of connections, 1933c, p. 248) and *C* (principle of reciprocity of connections, 1933c, p. 249), which, with but few exceptions, are also found in every part of the central nervous system.

It is an immediate consequence of the anatomy of the preparation that shocks through electrodes F or Col by stimulating axons or cells set up a volley of impulses, called *f* or *c* according to the electrodes used, which, after conduction, is delivered to the motoneurons. Furthermore the *f* or *c* volley is also

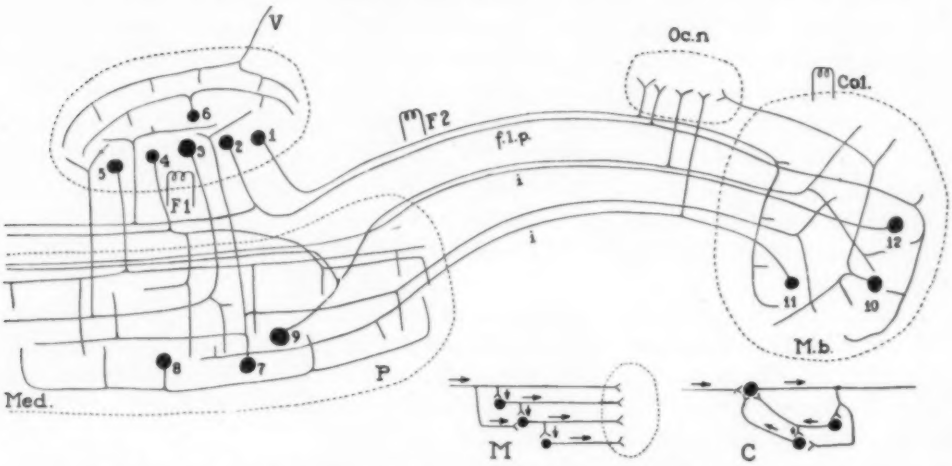


FIG. 2. Diagram of the pathways connecting the internuncial cells among themselves and with the ocular motoneurons. V, vestibular nerve; *1* to *6*, cells in the primary vestibular nuclei; 7, 8, 9, cells in the reticular formation in the medullar (Med.) and pons (P.); 10, 11, 12, cells in the reticular nuclei in the midbrain (M.b.); Oc.n., oculomotor nuclei; f.l.p., fasciculus longitudinalis posterior and similar pathways; *i*, internuncial pathways; F1, F2 and Col., position of the stimulating electrodes. The diagrams below indicate the two types of chains formed by internuncial cells; *M*, multiple and *C*, closed chain.

delivered to internuncial cells, which may respond and fire new volleys of impulses, necessarily delivered, at least in part, again to the motoneurons. In previous reports (1935a, to e) attention was paid especially to the effect of the *f* or *c* impulses. Here the effects of the internuncial impulses will be examined in greater detail.

TECHNIQUE

The experiments here presented have been made on the oculomotor preparation of the rabbit as previously described (1935a, e), the only difference being that in some experiments the responses were recorded from the trochlear nerve. The stimulating F electrodes on the floor of the fourth ventricle were placed in some experiments on the caudal part of the vestibular nuclei (position F1, Fig. 2), and in other experiments at the level of the abducens nucleus (position F2, Fig. 2). With electrodes in position F1, the number of impulses directly conducted to the motoneurons (*f*, Fig. 3) is smaller than with the electrodes in position F2, so that the response is extablished chiefly through the internuncial system. The cathode of the C electrodes introduced in the anterior colliculus was placed approximately as indicated in Fig. 2, Col.

Results

The records reproduced in Fig. 3 were obtained under conditions favoring internuncial discharge. The head of the rabbit was tilted some 40° upwards, so that there was a considerable tonic labyrinthine innervation of the superior oblique muscle, which revealed itself by small irregular waves of the electrogram of the trochlear nerve. The impulses started by a shock through electrodes F1 could thus summate with the constant stream of labyrinthine impulses maintaining the tonus of the superior oblique muscle. Single shocks of progressively increasing strength were delivered at two-second intervals.

For records *1* and *2* (Fig. 3) the stimulus was barely at threshold and there is an indication of response only in record *1;* but in records *3* and *4* the response was rather large. As in *1*, it consisted in a re-enforcement of the tonic waves lasting for some 4–5 msec. The response increased when the shock was strengthened (*5, 6, 7, 8*), with the peculiarity that the largest potential waves often appeared at about the middle part of the response. Further strengthening of the shock (*9, 10, 11*) to maximal (*12*) and hypermaximal value (*13, 14*) caused additional increase of the response. However, the increase of the early potential waves was not accompanied by increase of the late ones; on the contrary, the latest waves disappeared and the response became shorter (cf. records *13* and *14* with *6, 7* and *8*).

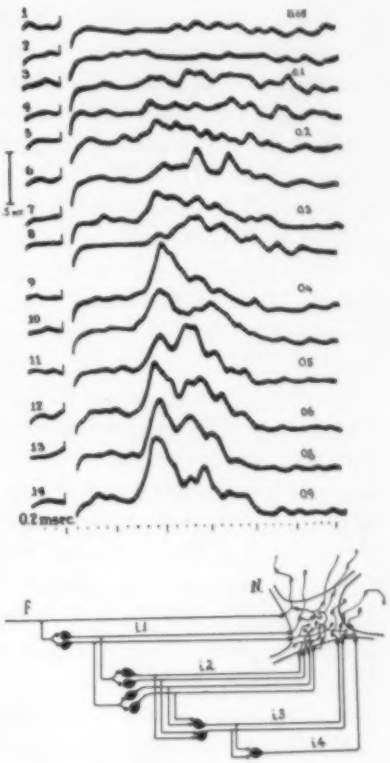


Fig. 3. Oculomotor preparation of the rabbit; responses recorded from the trochlear nerve. Stimulating electrodes in position F1 (Fig. 2.), (2-2-36). The numbers on the right hand side of the records indicate the strength of the shock in potentiometric units. The diagram below indicates the temporal and spatial distribution of impulses arrived at the motoneuron N after a shock is delivered to fiber *f; i*1, *i*2, *i*3, *i*4, internuncial paths. Passage of a synapse means a delay of about 0.6 msec. Note that each fiber has several synaptic knobs on the neuron, an arrangement increasing the possibility of spatial summation.

The type of response shown in records *1* to *8* of Fig. 3 is one that might be expected. The stimulating shock created a volley of impulses partly delivered to the motoneurons and partly to internuncial cells; some motoneurons responded to the volley and their impulses reached the recording electrodes. Some internuncials also fired and caused other motoneurons and internuncials to respond. Likewise, this second volley of internuncial impulses stimulated other motoneurons and internuncials to discharge impulses into their axons, etc. The process was completed when the

internuncial volleys failed to reach threshold value for the next neurons. Since the average synaptic delay of internuncial cells is about 0.7 msec., it is fair to assume that responses such as those shown in records *7* and *8* had involved passage of the impulses through four or five internuncial neurons.

What *a priori* could not be expected is that strengthening of the shock, *i.e.*, increase of the size of the *f* volley, would cause the response to lose the late waves (records *9* to *14*). This has only one explanation, namely, that the motoneurons, which in weak responses fired upon arrival of late internuncial volleys, in response to strong shocks fired when stimulated either by the impulses of the initial (*f*) volley or by the early internuncial volleys, and they could not fire again for the remainder of the response. The late internuncial volleys were lost because they were delivered to refractory neurons.

This result is expressed in graphic form in the diagram at the bottom of Fig. 3. The fiber marked *f* belongs to the posterior longitudinal bundle and is supposed to reach a motoneuron eventually engaged in the response to the F shocks. *i.1.*, *i.2.*, *i.3.*, and *i.4.* are those few internuncial pathways which are crossed by the impulses in their way to the motoneurons. It is seen in the diagram that if the motoneuron (N.) does not respond to the *f* impulses, it may respond to the internuncial impulses after a latency equal to one, or to the sum of several synaptic delays; but if it is fired by the *f* impulses it will not reappear in the response as long as the *i* impulses find it in a refractory state.

Since even the strongest responses (*12* to *14*) contained only a small fraction, *i.e.*, scarcely one-third, of the total cell population of the motor nucleus, the diagram also illustrates the fact that the internuncial volleys were delivered in great density again and again to a small number of neurons, or in other words, that despite the many possible channels for conduction into branches (Figs. 1 and 2) the impulses remained confined within a few selected channels, so that the majority of the neurons of the motor pool received only subthreshold stimuli. Using a term introduced by the Oxford school (Cooper, Denny-Brown, and Sherrington, 1926) it may be said that during activity the internuncial and motor pools become *fractionated* into active and inactive groups, part of the latter group constituting a *subliminal fringe* (Denny-Brown and Sherrington, 1928), the activation of which demands stimulation by another set of pathways. In the particular case under consideration the fractionation was already established by the tonic labyrinthine innervation in which, as in other tonic innervations (cf. Denny-Brown, 1929; Adrian and Bronk, 1929), a small number of motoneurons are continuously engaged. Apparently the shock delivered to the posterior longitudinal bundle and other secondary vestibular paths temporarily altered the fractionation by causing some motoneurons of the subliminal fringe to enter into the active group. But still the additional impulses were unable to reach the threshold of neurons that were not already in the subliminal fringe. As a result, when a large number of the facilitated motoneurons responded (Fig. 3, *12* to *14*), the later internuncial volleys became ineffective.

The diagram of Fig. 3 deserves especial consideration because it repre-

sents the relatively simple type of chains of neurons in which the internuncial system becomes fractionated during transmission of impulses. It has been substantiated by a number of other experiments. That the impulses of successive internuncial volleys actually are delivered repeatedly in great numbers to a small number of motoneurons is demonstrated in a most conclusive manner by the records in Fig. 4 obtained by successive delivery of two F1 shocks. Either shock alone (records *1* and *2*) set up a response as in Fig. 3, *10* and *12* respectively. When both shocks were delivered in succession at intervals of 0.5 msec. or more, the response to the second shock increased considerably, but only in its early wave; the late waves were considerably reduced even when the facilitation was greatest (record *5*). At that moment the response to the testing shock became a practically synchronous spike somewhat less than half the maximal nerve spike. As there can be no doubt that the testing *f* volley was followed by successive volleys of internuncial impulses, the lack of late waves in the facilitated response demonstrates that the *i* impulses were delivered to the same motoneurons that had responded to the *f* volley.

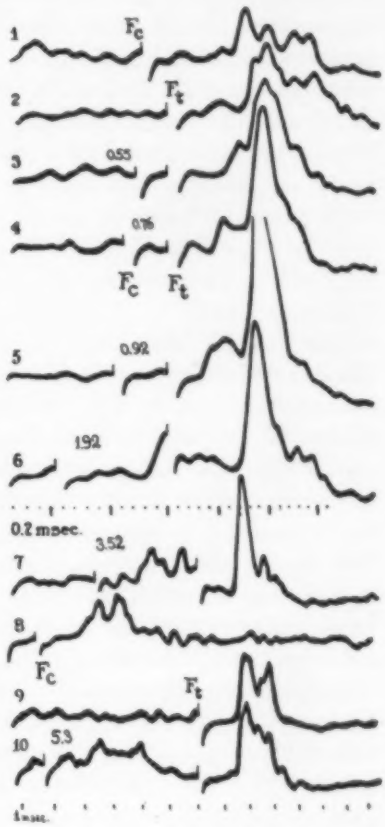


FIG. 4. From the same experiment as in Fig. 3. Two F1 shocks are delivered at the intervals indicated on the records. *1* and *8* reproduce the conditioning and *2* and *9* the testing responses in isolation.

Records *7* to *10* correlate the duration of the period of facilitation and the duration of the response to the conditioning shock. As shown by record *8*, the total duration of the conditioning response was about 4–5 msec., which also was the duration of the period of facilitation. In record *7*, where the interval between shocks was 3.52 msec., the facilitation was still great; but in record *10*, where the interval was 5.3 msec., there was no appreciable increase of the testing response. Evidently in the oculomotor preparation the increase in strength of stimulation necessary to bring motoneurons of the subliminal fringe into the active group is so small (cf. 1938c) that unless some motoneurons are engaged in the response, the extension of the subliminal fringe is negligible.

Since the period of the summation of impulses delivered at different synapses is extremely short (1935c, d; for sympathetic ganglion cells see Eccles, 1937b), there can be no doubt that the height of the initial wave in the facilitated response (records *3* to *7*) measures the number of inter-

nuncial impulses entering the motor nucleus at different moments after delivery of the conditioning F shock. The testing volley of *f* impulses was of course constant, because the testing shock was maximal, and consequently the number of responding motoneurons was roughly proportional to the number of *i* impulses arriving at the motor nucleus simultaneously with the *f* impulses. The temporal course of facilitation demonstrates that the internuncial volleys had more or less the densities indicated in the diagram in Fig. 3, the largest volleys being i_1 and i_2 after the impulses had crossed through one or two internuncial neurons.

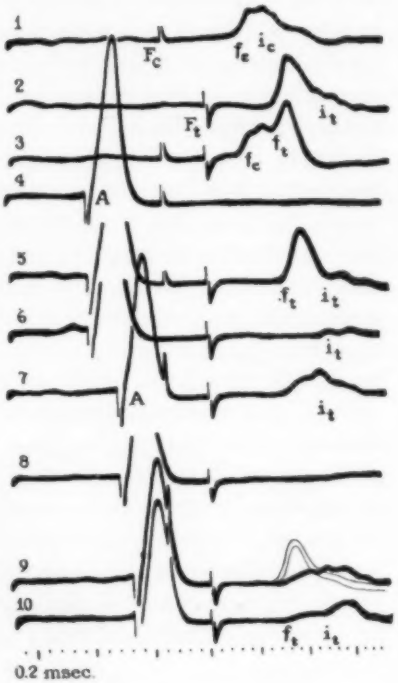


FIG. 5. Oculomotor preparation; responses recorded from the trochlear nerve. Stimulating electrodes in position F2 (Fig. 1) (2-5-36). F_c and F_t, conditioning and testing F shocks: f_c and f_t, responses to the F_c and F_t volleys; i_c and i_t, responses to internuncial impulses; A, maximal antidromic shock and its response. In record *9* the unconditioned f_t response has been reproduced (in light tracing) on the conditioned one. Records *1* to *6* were obtained at slightly higher amplification than records *7* to *10* (cf. height of the A responses).

The records in Fig. 5 obtained in another experiment also are very demonstrative. In this experiment the electrodes were placed in position F2 (Fig. 2), with the result that the initial *f* volley was large enough to cause the appearance of a considerable *f* wave, while the waves of internuncial origin were small (Fig. 5, *1*, *2*). Nevertheless, it could be demonstrated that the *f* volley was followed by powerful *i* volleys which remained ineffective because they were delivered almost exclusively to those motoneurons that had been made refractory by their response to the *f* impulses. The experiment was based on the following argument (1936, Fig. 4; cf. Eccles, 1931, p. 582). An antidromic shock was delivered to the motor nerve in order to create refractoriness of the motoneurons, and at different moments during the period of recovery an F response was elicited. The impulses of the initial *f* volley reached the motoneurons while their threshold was still high and failed to elicit responses, but the *i* volleys, which arrived at the motor pool after delays of 0.6 msec. or more, found the motoneurons at a more advanced state of recovery and were able to set up responses. By properly choosing the interval between the antidromic and the F shocks it was possible to obtain F responses in which the *f* wave was small, while the *i* waves were large (Fig. 5, *9*, *10*); as the rate of recovery of the motoneurons is rather slow (1935c; Lorente de Nó and Graham, 1938), it must be concluded that the *i* volleys were almost as

strong as the *f* volley, although in strong unconditioned F responses (Fig. 5, *2*) the *i* waves were practically absent.

The actual experiment is illustrated by the records shown in Fig. 5. Two F2 (Fig. 2) shocks (F_c and F_t) were delivered in succession at the constant interval of 0.8 msec., and a maximal antidromic shock was delivered at three different intervals (1.30, 0.8, and 0.6 msec.) before the first F_2 shock. Both the conditioning (Fig. 5, record *1*) and the testing shock (record *2*) set up responses with a large *f* wave followed by small *i* waves; but in a similar manner as in the experiment of Fig. 4 when the F shocks were delivered in succession, the *i* waves in the response to the testing shock disappeared (record *3*).

The maximal antidromic shock when delivered 1.30 msec. before F_c prevented any response to this shock (record *4*); but when F_c was followed by F_t, the response to the latter contained a large *f* wave (with slightly lengthened latency) and, in striking contrast with the response in record *3*, also well marked internuncial waves (i_t). When F_c was omitted, the response to F_t (record *6*) contained only *i* waves.

When the antidromic shock was approached to the F_c shock (record *7*) the response to F_t changed in a spectacular manner; the early f_t wave decreased, while the internuncial waves increased considerably. If F_c was omitted no response was obtained (record *8*). Further decrease of the interval between the antidromic and the F_c shock to 0.6 msec. resulted in a further decrease of the f_t wave, without reduction—there rather was an increase—of the internuncial waves (records *9* and *10*).

The fractionation of the internuncial and motor pools is maintained even in the case of repetitive stimulation creating strong activity. In the experiment illustrated by the records in Fig. 6 a rhythmic series of shocks was delivered through C electrodes (Fig. 2, Col). The responses were recorded from the left trochlear nerve and the C cathode was placed in the reticular formation in front of the left oculomotor nucleus. Since the nucleus of the left trochlear nerve is located on the right side, the shock did not stimulate trochlear motoneurons, but stimulated trochlear axons shortly after they had crossed the middle line. This response is labeled *n* on records *13, 14, 17*. Synaptic responses of trochlear motoneurons, labeled *s*, had of course a longer latency.

Single shocks of any strength or tetanic stimulation at low frequency failed to set up synaptic responses, but when the frequency of the series was raised (*1* to *9*) synaptic responses appeared after a period of recruitment including never less than three shocks; after a further period of increase, the responses remained at rather constant level, roughly proportional to the frequency of the series.

The recruitment was obviously attributable to the same process which underlies the facilitation of responses of motoneurons to two shocks in succession (1935c, e). The first shock created impulses which lowered the threshold of some internuncial cells to synaptic and electrical stimuli; therefore the second shock was able to stimulate a larger number of internuncials and create

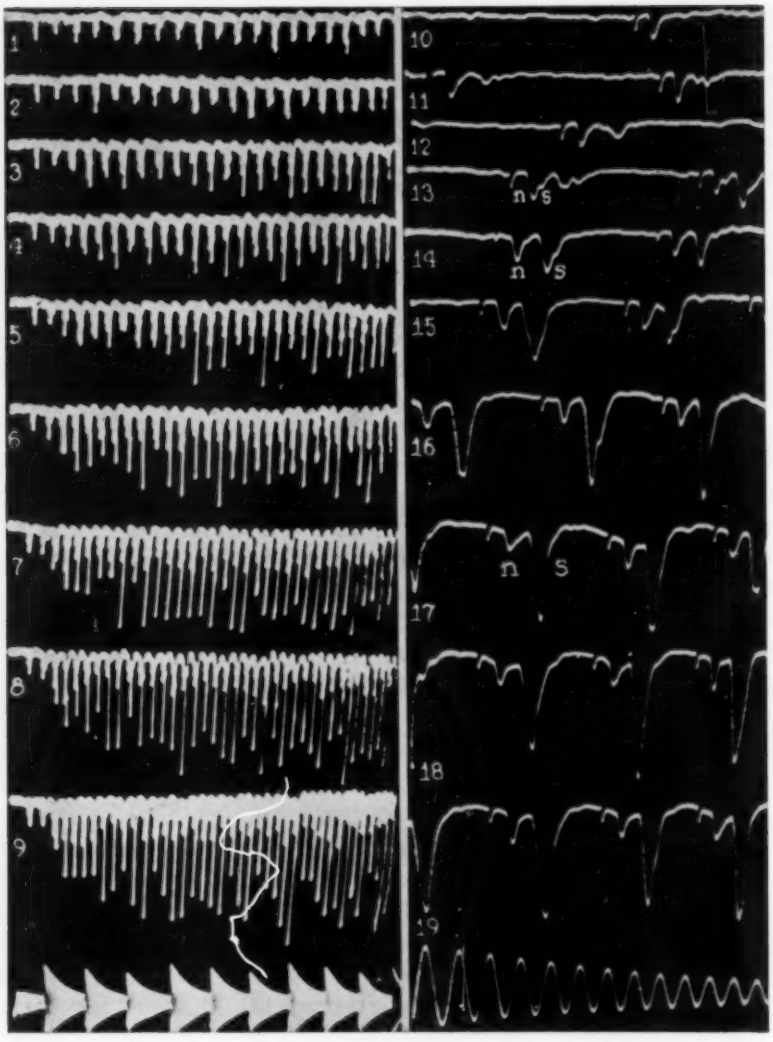


FIG. 6. Oculomotor preparation; responses recorded from the trochlear nerve. Electrodes in position Col. (Fig. 2) (3-9-36). Tetanic stimulation. The records on the right side were obtained at higher sweep speed than those on the left. Time (1/60 and 1/1000 sec.) below each series of records. Note that downwards deflection indicates negativity at the active electrode. *n*, response of directly stimulated trochlear fibers; *s*, synaptic responses.

a greater facilitation of the third shock, etc. The process was cumulative and soon the internuncial bombardment became large enough to enable the motoneurons to respond to the impulses of the direct volley (*c*) of impulses started by each C shock in internuncial axons or cells (cf. discussion, *e*). However, the recruitment did not progress beyond a certain limit; here as in the case of reflex responses fractionation took place. In fact the responses in the

experiments of Fig. 6 did not include more than a third of the total number of cells of the motor pool.

An analysis of the response can be made on the basis of records *10* to *19* which contain the middle part of responses similar to those on the left side, photographed at higher sweep speed.

At frequencies of less than 100 per second there was no synaptic response following the *n* wave (*10*), but at the frequency of 120 per second (*11*) the *n* wave began to be followed by an asynchronous synaptic response including several wavelets. The same type of response was observed at frequencies up to 145 per second (*15*). In terms of the diagram in Fig. 3 this type of response indicates that the initial volley of *c** impulses was sufficient to reach the threshold of only a small number of motoneurons, while the following i_1, i_2, etc., volleys were able to fire a larger number. It is important to note that in record *13* the synaptic response, despite its small size, appeared after the minimal synaptic delay (cf. 1938b).

Increase of the frequency of the series resulted not only in an increase but also in a shortening of the duration of the synaptic response, which soon (*17* to *19*) became a synchronous spike. Evidently the *c* impulses set up by each C shock met at the motoneurons a large internuncial volley due to the preceding shock and were capable of firing a large number of motoneurons. The following *i* volleys, being delivered with great density only to refractory neurons, failed to set up new responses. Here again, as in the previously studied, cases despite the great internuncial activity the *i* impulses arrived in large numbers only at a discrete number of neurons.

The fractionation of the motor nucleus was accentuated by the progressive increase of threshold (summation of subnormality) of the neurons engaged in tetanic activity. Although there is no conclusive proof, it is most likely that the motoneurons were following each shock of the series. As indicated by records *10* to *15*, at low frequencies some motoneurons, obviously those near the subliminal fringe, alternated; but at higher frequencies the motoneurons must have followed every shock, otherwise some of them would have responded after the minimal synaptic delay, as in record *13*, and not after the maximal delay, as in records *17* to *19*. The frequency of the series necessary for effective recruitment was well above the critical one for summation of subnormality, *i.e.*, about 100 (cf. Lorente de Nó and Graham, 1938) so that once the motoneurons responded to two shocks in succession, their threshold became so high that they could respond again only to very strong stimuli, which apparently were created only by the coincidence of a *c* and an *i* volley. In the absence of *c* volleys, the *i* volleys would have been subliminal for any of the motoneurons engaged in the response. And in fact it is consistently found in experiments of this type that, despite the strong internuncial activity

---

* The volley of impulses set up by direct stimulation of axons or somata of internuncial neurons is called *f* or *c* according to the position of the stimulating electrodes (F or Col. Fig. 2). Later volleys which cross through one or more internuncial synapses are always called *i*.

created by the tetanus, after the end of the series of shocks the electrogram of the nerve, or muscle, showed a silent period of some 15 to 20 msec. duration, followed by a long-lasting tonic discharge (Fig. 9, *5*, *13*).

Experiments such as that illustrated by the records of Fig. 4 make the assumption likely that facilitation ends when the internuncial bombardment ceases. However, this demands careful consideration, because according to the observations of Eccles (1936a, b, 1937b), subliminal stimulation of the ganglion cell after the period of effective summation of impulses arriving at different synapses—called by Eccles "period of summation of detonator responses," produces a long-lasting state of lowered threshold (Eccles' *c.e.s.*). The fact must also be considered that the duration of the period of effective summation has been determined by studying the interaction of only two volleys of impulses, and it is thinkable that continued bombardment may lead to different results because it might produce a cumulative change in the motoneuron.

With ocular motoneurons it has as yet been impossible to demonstrate the existence of an enduring effect of subliminal impulses comparable to Eccles' second phase of facilitation (*c.e.s.*), perhaps because in the cases studied internuncial bombardment and facilitation were inseparable. An instructive experiment will be mentioned here.

The series of records in Fig. 7 illustrate one type of interaction of F and C shocks. In isolation the F shock (*3*, *5*, *18*) caused the appearance of a response as shown in Fig. 3; the tonic discharge down the trochlear nerve was increased during a period of several msec. The C shock, however, caused a response composed of an almost synchronous spike potential followed by a silent period of several msec., during which the tonic discharge ceased (*1*, *2*, *7*, *21*).

The F and the C shocks may have in part stimulated the same fibers, but there can be no doubt that they also stimulated different internuncial axons, because when delivered at simultaneity (*22*) more neurons responded than when either shock was delivered in isolation. When the F preceded the C shock, the response to the latter was facilitated (*4* to *12*), the period of facilitation lasting as in Fig. 4 through the period of increased tonic activity which followed the initial *f* discharge.

The results were different when the C preceded the F shock. At an interval of 0.2 msec. (*20*) the F response was greatly reduced even in its early wave, and it was practically abolished at an interval of 0.49 msec. (*19*). At greater intervals (*17*, *16*, *15*, *14*, *13*) the F response was totally abolished, as was the case also when the C response included only a small number of motoneurons (*15*). The F response began to reappear at an interval of about 4 msec. between shocks, and up to the last interval studied (5 msec.) it did not show signs of being facilitated.

The effect stated cannot be ascribed to the presence of some "inhibitory" impulses in the C volley, because when the F and the C shocks were delivered simultaneously (*22*) there was a marked summation. The assumption of "inhibitory" impulses in later internuncial volleys following the initial *c* volley also would be in conflict with the results of the experiment shown in Fig. 6

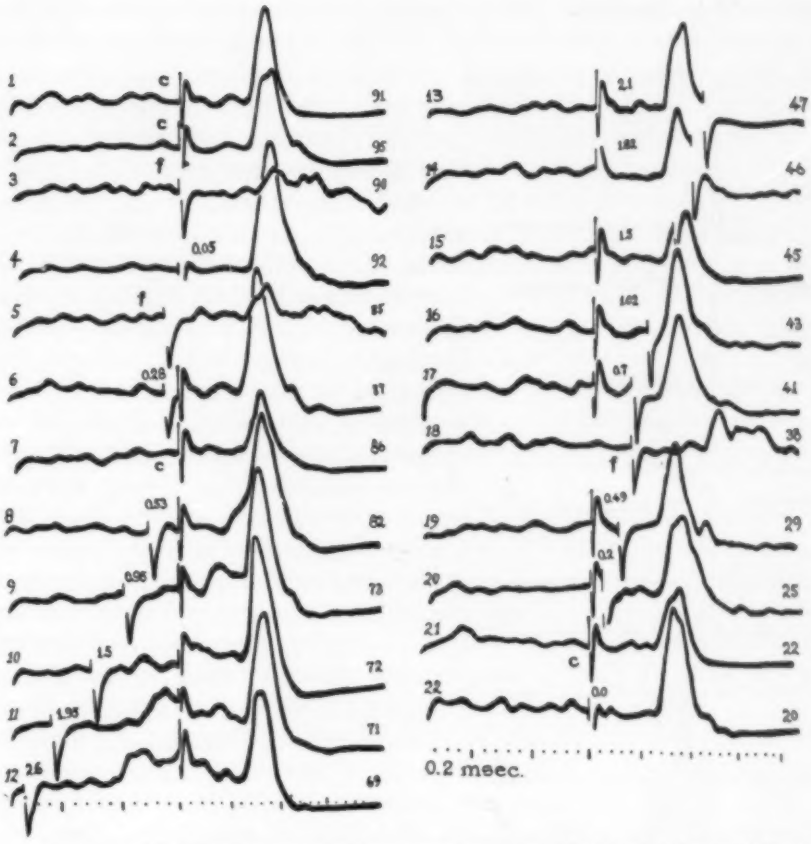


FIG. 7. Oculomotor preparation; responses recorded from the trochlear nerve. Two stimulating electrodes in positions F1 and Col. (Fig. 2) respectively (same experiment as in Figs. 3 and 4). The responses to the C and F shocks in isolation have been reproduced in records *1, 2, 3, 5, 7, 18,* and *21.* There was a certain variation of height of the C response due to the discontinuous character of the tonic labyrinthine innervation, the response being of course larger when the *c* impulses happened to coincide with a large internuncial volley. Record *1* reproduces the largest observed response to a C shock in isolation. The numbers of the right hand side of the records indicate the order in which they were obtained; between each two consecutive records there was an interval of two seconds. For records *4* to *12* the F shock preceded the C shock at the intervals indicated in msec. on the records. For records *13* to *22* the C shock preceded the F shock. Time in 0.2 and 1. msec. below.

and of other experiments, in which it was found that the C shock may create a long-lasting facilitation of the F shock. For example, Fig. 8 reproduces records from an experiment in which the C shock was followed by a markedly enduring facilitation of the F response (*1, 3, 4, 6*), greater than the facilitation of the C response by the F shock (*9, 10*).

The striking difference between the experiments in Fig. 7 (*13* to *20*) and Fig. 8 (*1, 3, 4, 6*) finds its explanation in the fact that in Fig. 8 the C response

was followed by a period of increased tonic activity, obviously due to internuncial bombardment, while in Fig. 7 the C response was followed by a silent period which indicated absence of internuncial bombardment; even the transmission of the tonic labyrinthine impulses had been blocked. Evidently the *c* volley in this experiment was not followed by internuncial volleys; while it arrived as well at motoneurons as at internuncials, the latter failed to respond, or if they did respond their impulses were blocked at some internuncial link made refractory by the shock (cf. 1936). Since the *f* volley, no matter how powerful it may be, in the absence of a background of subliminal stimulation cannot set up response in any motoneuron, the F response became "inhibited" as soon as the period of summation of the *c* and *f* volleys was finished. Comparison of records 20 and 21 demonstrates that summation was poor, indeed scarcely possible when the *c* and *f* volleys were delivered 0.2 msec. apart. This result and the "inhibition" of the F response in records 13 to 17 do not demonstrate that the *c* impulses did not cause a long-lasting lowering of threshold of some motoneurons, but they do demonstrate that if a long-lasting effect such as this had been produced, it was considerably weaker than the immediate effect of a mild (*i.e.*, subliminal for the majority of the motoneurons), internuncial bombardment.

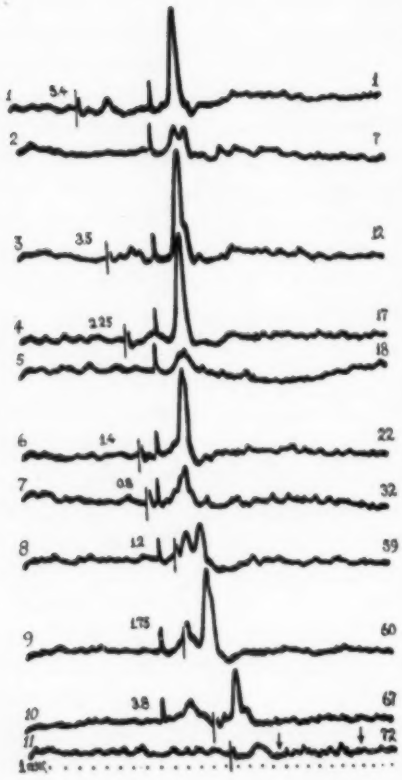


FIG. 8. Oculomotor preparation; responses recorded from the trochlear nerve (3-3-36). Two stimulating electrodes in positions F2 and Col. (Fig. 2) respectively. The F shock was maintained at the center of the oscillograph while the C shock was made to appear before (*1* to *8*) and after (*9* and *10*) the F shock at the intervals indicated in msec. on the records. *2*, response to the F shock in isolation; *11*, response to the C shock in isolation; note the increased tonic activity (between vertical arrows) following the c response. Time in msec. below.

The limited strength of durable effects also is apparent after long-lasting bombardment of the motoneurons, as in the case of vestibular nystagmus. During that reflex the agonistic eye muscles show a series of slow contractions of long duration, interrupted by rapid relaxations of short duration—no more than 100 msec. Thus, it may be said that the motoneurons are submitted to a constant bombardment by impulses interrupted by short periods of no bombardment. Should continued bombardment after it stops be followed by a long-lasting lowering of threshold, then during the periods of relaxation at least those motoneurons which did not fire during the

nystagmic contraction would respond to F shocks. But in fact they do not so respond; the response to an F shock is always large during the periods of contraction, while it is small or absent during periods of relaxation (1935a, Fig. 2).

Under the conditions of the present experiments, in which the stimulating shock always creates a powerful volley of impulses delivered to the motoneurons, facilitation and increase of the tonic waves in the electrogram of the motor nerve or the muscle have been inseparable phenomena, even when facilitation lasted for several seconds. For that reason, facilitation in every case could be explained as the result of instantaneous summation of the testing volley of impulses with impulses of the internuncial bombardment, the existence of which was revealed by tonic discharge of some motoneurons. Fig. 9 reproduces records from a representative experiment in which long-lasting facilitation was observed after a short tetanic stimulation through the C electrodes. In order to avoid strong motor reactions the preparation was kept under light ether narcosis, which is known to reduce the tonic internuncial activity.*

Although during ether narcosis single F shocks are ineffective (Fig. 9, *11*, *16*) two F shocks in succession may set up strong responses (Fig. 9, *1*), undoubtedly because the first shock starts an internuncial bombardment of the motor nucleus. Its duration is usually brief (from 1.25 to 5 msec.), the impulses being able to cross only a few internuncial synapses, but tetanic stimulation leads to the creation of internuncial bombardment and facilitation of several seconds' duration (Fig. 9).

As already mentioned, in the experiment illustrated by the records in Fig. 9 the conditioning tetanus was delivered through C electrodes, the C cathode being placed in front of the oculomotor nucleus, but far enough away to prevent electrical stimulation of motoneurons or motor axons. The response was recorded from the right internal rectus muscle. A series of C shocks at low frequency (Fig. 9, *2*, *3*) did not cause motor response or long-lasting facilitation of F shocks, but series of low frequency during the period of increased internuncial activity following a previous stimulus, or series at high frequency caused motor responses similar to those in Fig. 6 and also long-lasting facilitation of the F shock (Fig. 9, *5*, *8*, *13*). During the period of facilitation, except in the silent period immediately following motor discharge, the electrogram of the muscle showed tonic waves caused by the response of a few motoneurons. Facilitation was strong while the tonic discharge was great (*6*, *9*, *14*), but it decreased when the tonic waves diminished in size (*7*, *10*, *15*), and disappeared when the tonic waves ceased (*11*, *16*). It is important to mention

* The effect of ether is rapidly apparent; it has, in fact, been observed after 15 seconds of inhalation of a mixture of ether and air so weak that it did not cause disappearance of the corneal reflex after prolonged inhalation. A specific action of ether on some neurons of the vestibular system must, therefore, be assumed. However, the motoneurons are but little affected, because they readily respond when internuncial bombardment is created by suitable stimulation. Furthermore, results similar to ether narcosis are obtained when the background of subliminal stimulation is suppressed by destroying the reticular substance in the pons. The selective effect of anesthetics is also suggested by the experiments of Bremer and Moldaver (1933).

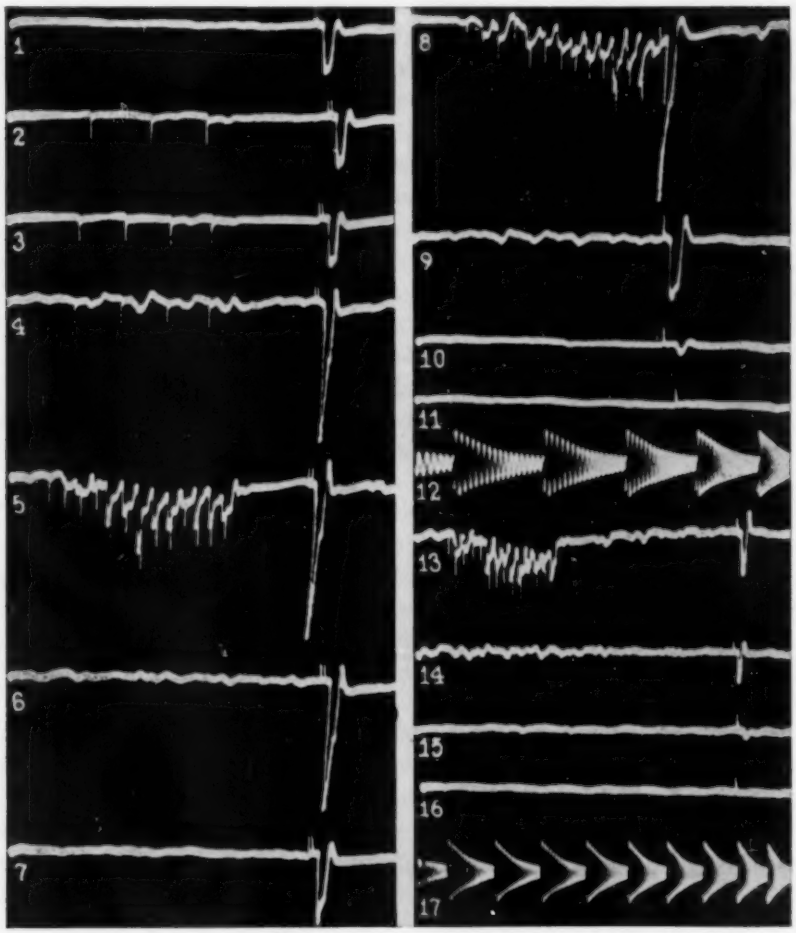


FIG. 9. Oculomotor preparation; responses recorded from the internal rectus muscle (negativity downwards). Two stimulating electrodes in positions F2 and Col. (Fig. 2) respectively (6-5-36). Light ether narcosis. *1*, response to two F shocks in quick succession; *2*, *3*, the same response conditioned by a series of shocks through the C electrodes at low frequency; *4*, the same as *3* but the series delivered during a period of internuncial activity following a previous C stimulation at high frequency. The F response is facilitated. *5*, facilitation by a series of 13 C shocks at a frequency of 500 per second; *6*, two seconds later; *7*, four seconds later. Note the tonic activity in records *6* and *7*. *8*, *9*, *10*, *11*, facilitation of the response to one F shock immediately and 2, 4 and 6 seconds after a series of 13 C shocks at a frequency of 475 per second. Note that the F shock remained ineffective (*11*) when the electrogram of the muscle did not reveal the existence of tonic discharge. *12*, timing film (1/60 and 1/1000 second) for records *1* to *11*; *13*, *14*, *15*, *16*, a similar set of records, also obtained at two second intervals, illustrating facilitation of a subliminal F shock (*16*) after delivery of tetanic stimulation (*13*) through the C electrodes; *17*, timing film (1/60 second) for records *13* to *16*.

that each facilitated response (*6, 9, 13*) was followed by a silent period in the electrogram, indicating that the impulses set up by the F shocks fired those motoneurons which were taking part in the tonic discharge. Here again facilitation extended only to the motoneurons reached by large internuncial volleys.

In view of the evidence presented here the conclusion must be reached that the internuncial bombardment, despite the short duration of the effect

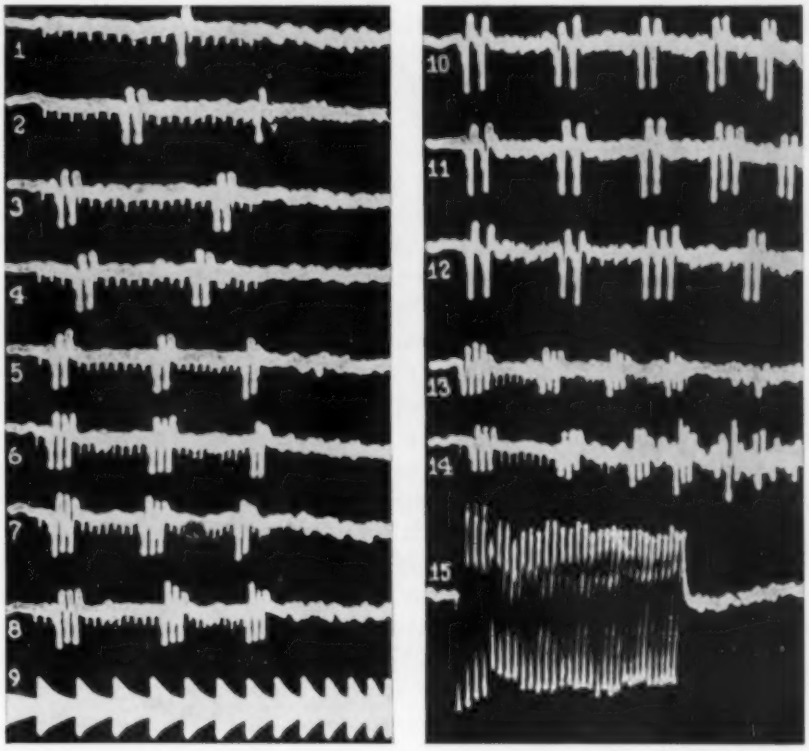


FIG. 10. Oculomotor preparation; responses recorded from the internal rectus muscle (negativity downwards) (6-1-36). Tetanic stimulation through the C electrodes. Time (1/60 second) in record *9*. The small sharp downward deflections are shock artifacts. Further explanation in text.

of the individual impulses, constitutes a statistically constant stimulus for the motoneurons of the active group; each neuron responds to it rhythmically at a frequency determined by two factors: (1) strength of the bombardment and (2) rate of recovery of the neuron. An almost ideal confirmation of this conclusion is given by the records in Fig. 10. The cathode of the stimulating (C) electrodes was placed near the oculomotor nucleus, so that certain motoneurons were capable of responding to the summated effect of induction shocks and internuncial impulses.

In records *10*, *11*, and *12* the shocks were strong enough to stimulate some motoneurons. The responses did not, however, follow the rhythm of the stimulating series; they appeared in groups of two and sometimes three responses, separated by intervals including four or five shocks during which only a mild tonic discharge was visible. The grouping of discharges was obviously attributable to summation of subnormality; two or three responses in quick succession raised the threshold of the motoneurons to a high level and no further response could take place until the threshold had recovered.

In records *1* to *8* the strength of the shocks was reduced so that they did not reach the electrical threshold of the motoneurons without first increasing the internuncial bombardment. The frequency of the stimulating series was progressively increased from record *1* to record *8*. In record *1* the electrical threshold of the motoneurons was not reached until the tenth shock of the series, and it was not attained again during the remainder of the series. In record *2* the response appeared earlier (seventh shock) and there was a grouped discharge followed by a long silent period. A similar effect is seen in records *3* and *4*. In record *5* the frequency of the series was sufficient to create a strong internuncial bombardment, with the result that the responses were regularly grouped in pairs. Nevertheless two responses in quick succession were sufficient to create a subnormal threshold which remained for periods of over 40 msec. above the stimulating value of the shocks.

Further increase in the frequency of the series (*6*, *7*, *8*) reenforced the internuncial bombardment to a degree so that the groups of responses contained three equal twitches, but here again after the third twitch the threshold of the motoneurons became so high that a silent period, of 40–50 msec. duration, followed each third twitch. While records *1* to *12* were being taken, the preparation was kept under mild ether narcosis which prevented the increase of internuncial activity above unwanted limits; but before taking records *13* to *15*, the narcosis was discontinued. The strength of the shocks was reduced below the value used for records *1* to *8;* nevertheless the groups of responses contained three or four twitches before subnormality increased sufficiently to prevent further response. The great amount of internuncial activity created by the series of shocks also revealed itself in the powerful tonic discharge lasting throughout the series.

Although the records were obtained at two-second intervals, the effect of the stimulus was cumulative and the tonic discharge at the end of the series increased progressively in each record (*13*, *14*). Finally, in record *15* the internuncial bombardment was so great that the three first shocks of the series reached the threshold of all the motoneurons of the nucleus, resulting in an abortive group formation; but the internuncial bombardment raised the stimulating effect of the shocks to maximal value and the remainder of the response consisted of maximal twitches at the frequency of the series. The internuncial activity was so great that despite the high threshold of the motoneurons no silent period appeared after withdrawal of the stimulus. Furthermore it continued to increase and soon spread through the whole

reticular formation, with the result that the preparation showed violent convulsions.

The grouping of discharges also may be observed in the pure synaptic responses of motoneurons. In the experiment shown in Fig. 11 the responses were recorded from the right trochlear nerve; the C cathode was placed in front of the right oculomotor nucleus. In record *1* the frequency of the series (about 300 per second) was almost subliminal, only two small responses being present after the sixth and the tenth shock. Strong responses began to appear

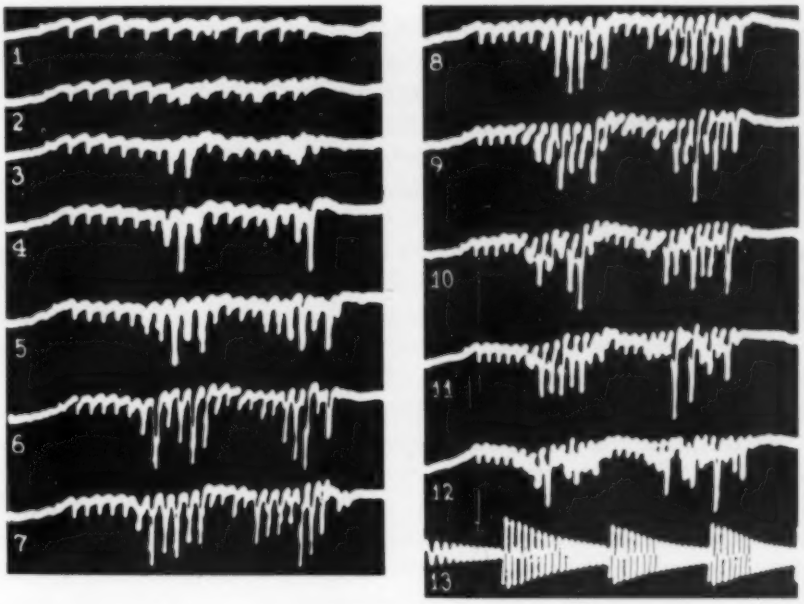


FIG. 11. Oculomotor preparation; responses recorded from the trochlear nerve (negativity downwards (2-13-36). Tetanic stimulation through the C electrodes. Time (1/60 and 1/1000 second) in record *13*. The small sharp downward deflections are shock artifacts. Further explanation in text.

in record *3* when the frequency of the series was about 350 per second; the discharge of the motoneurons took place in two groups separated by an interval of about 15 msec. Increase in the frequency (*4*, *5*, *6*) caused the responses to appear early and to grow in size, but it did not change the grouping of the discharge. At high frequencies the discharges, although clearly grouped as before, became irregular (*11*, *12*).

The mechanism of the production of groups is understandable. Single shocks being ineffective to create sufficient impulses to reach the threshold of the motoneurons, successive recruitment was necessary, until finally the internuncial bombardment became strong enough to bring the threshold of the motoneurons down to the stimulating value of the volleys created by the C shocks. But the tetanic activity of the internuncial neurons soon created in them a high threshold, with the result that the internuncial impulses were

blocked at some of the cells and the bombardment ceased. Response of the motoneurons could not take place until after a second period of recruitment. This effect is very interesting in that it reveals the existence of a process by means of which a pool of internuncial neurons may reduce the frequency of the impulses it transmits at the same time that it changes the character of the afferent stream from a practically continuous bombardment by asynchronous impulses into a series of powerful volleys of synchronous impulses at low frequency.

Discussion

(a) *Bombardment of motoneurons by internuncial impulses as a source of continuous stimulation.* The period of summation of the impulses arriving at neighboring synapses is short. For example, in the experiment illustrated in Fig. 7, *20* and *21*, most of the *f* and *c* impulses failed to summate and to reach threshold when delivered at 0.2 msec. intervals. Nevertheless internuncial bombardment may constitute a constant stimulus, because the great number of internuncial cells ensures the delivery of impulses in large numbers and at high frequencies. For example, in the case of Fig. 3, following the initial *f* volley, internuncial impulses entered the motor nucleus in successive volleys at intervals of about 0.7 msec., which is the average delay of internuncial neurons. Furthermore, the internuncial volleys, owing to slight differences in the delays at the individual neurons and to differences in the speed of conduction in axonal branches of various calibers, necessarily were highly asynchronous. The frequency of arrival of the impulses at the individual neurons was correspondingly high, for the frequency of the wavelets in records *5* and *6* in Fig. 3 was over 2000 per second, and the majority of the internuncial impulses remained below threshold for the motoneurons. Thus it may be said that the internuncial impulses arrive at the individual motoneurons in a constant stream, so that the *f* impulses created by the second, testing, F shock, delivered at any moment during the period of facilitation which follows the conditioning shock, always meet at the motoneurons internuncial impulses with which they can sum. The situation is exactly the same for the internuncial neurons, because as previously mentioned (Fig. 2), all the fibers having synapses on motoneurons also have synapses on internuncial cells, so that whenever motoneurons receive impulses at their synapses, internuncial neurons necessarily are also stimulated.

The shortness of the period of effective summation of two impulses excludes the possibility of the summation of impulses that have arrived in succession through the same fiber. Hence the strength of the stimulation by internuncial bombardment depends upon the density of the latter, *i.e.*, on the number of fibers conducting impulses simultaneously; and all gradations are possible, ranging from subliminal (*i.e.*, only maintaining facilitation) to liminal (*i.e.*, causing discharge of resting neurons) and supraliminal (*i.e.*, causing discharge of refractory neurons). Internuncial bombardment must necessarily cause rhythmic discharge of motoneurons, because each responding motoneuron will fire again as soon as its threshold is reached by the stimulus.

Internuncial bombardment (Forbes, 1922; but cf. Forbes, 1934, 1936) has all the properties of *c.e.s.* (Sherrington, 1925; Eccles and Sherrington, 1931b; Bremer and Homès, 1932), and since a motoneuron despite any possible lowering of threshold due to previous, intrinsic or extrinsic activity does not fire unless impulses are delivered to its synapses (cf. 1938b), there is no doubt that the "central excitatory state" leading to motor discharge is due to internuncial activity and bombardment. Furthermore, it has been shown in this paper that subliminal *c.e.s.*, *i.e.*, excitation demonstrable only by its ability to facilitate the response to an intercurrent stimulus, is always accompanied by internuncial bombardment, which under the conditions of the present experiments overshadows the effect of any other factor capable of lowering the threshold of the neurons.

For this reason the present discussion is conducted on the following principles: *The mechanism of the stimulation of neurons is the delivery of impulses at their synapses. The effect of the individual impulses is brief, but the continuous arrival of impulses ensures constant stimulation. The neuron responds whenever the stimulating effect of the impulses that arrive within a period of effective summation reaches its threshold.* The neurons as well as their axons (Gasser, 1935a, b; cf. Eccles, 1936b, p. 392) have two thresholds, the resting and the subnormal threshold which develop during tetanic activity (Lorente de Nó and Graham, 1938). The creation of a high subnormal threshold does not necessarily demand a long-lasting activity; two discharges at high frequency are sufficient to raise the threshold of the motoneurons to a high level (*loc. cit.*, Figs. 5 and 6).

The existence of a third threshold, even lower than the resting threshold, although it has not yet been demonstrated for motoneurons is likely, because it has been found to exist with sympathetic ganglion cells, with the neuromuscular junction, and with nerve fibers. With sympathetic ganglion cells Eccles (1936a, b, 1937b) observed after delivery of subliminal synaptic stimuli at the end of the period of effective summation, which Eccles has called summation of detonator responses, a second period of summation termed by him *c.e.s.*,* that appeared to be caused by a lowering of threshold of the ganglion cells. It never resulted in the setting up of an impulse. Bremer and Kleyntjens (1937) offer convincing arguments in favor of the view that the process underlying this second period of summation is the same as the process responsible for the passage of a second impulse across the partly curarized neuromuscular junction of the frog (Bremer, 1930; Bremer and Homès, 1932), or the neuromuscular junction of the crab (Lucas, 1917).

With nerve (Gasser, 1938), a second period of summation after subliminal stimulation can regularly be demonstrated under certain conditions, for example, after tetanization. Therefore the assumption lies at hand that the second period of summation is a general property of excitable tissues which

* The suggestion of Eccles to apply the term *c.e.s.* to the second period of summation is not followed here, for the reason that the term has been widely used with a different significance.

may influence synaptic transmission. However, in blood-perfused trochlear nerve the second period of summation is not demonstrable unless the recovery curve shows a supernormal phase, or unless the nerve has previously been tetanized (1938e). Under ordinary conditions it is absent; absence of peripheral recruitment is shown in Fig. 6. On the other hand, the effect of the lowering of threshold during the second period of summation is qualitatively the same as a mild internuncial bombardment (cf. Bremer and Kleyntjens, 1937, Gasser, 1938), and consequently not demonstrable in the presence of the latter (cf. Eccles, 1936b, p. 376). Since under the conditions of the experiments reported here the internuncial bombardment is always present, there is no immediate need for considering the second period of lowered threshold; although it is realized that under given conditions it might play a pre-eminent role. For example, the remarkable observation of Kleyntjens (1937) made on the frog that tetanization of the motor nerve increases the reflex response, indicates that at least under certain conditions, after prolonged tetanization a period of lowered threshold develops in the motoneurons. Another factor likely to play an important role in determining the threshold of the neurons is a change of metabolic conditions (Dusser de Barenne, McCulloch, and Nims, 1937). Its significance is not minimized by disregarding it in the present discussion, but more precise information is needed before it can be successfully considered in theoretical arguments.

The main difference between the concept of *c.e.s* as used by the Oxford school (Creed *et al.* 1932) and that of continuous stimulation by internuncial bombardment is that *c.e.s.* was assumed to develop and accumulate within the individual neurons, while internuncial bombardment places the excitatory and facilitatory mechanisms outside of the cell (1935b, p. 607). For many theoretical arguments the difference may be overlooked; in fact, the result obtained is essentially the same, whether the one or the other concept is used. In his review Eccles (1936b), while re-examining the physiology of the spinal cord in the light of recently acquired knowledge, found it necessary to alter but few of the original theoretical arguments. The concepts of recruitment, fractionation, subliminal fringe, etc. can be kept with their original meaning and have been repeatedly used in this paper. Nor is it necessary to alter the discussion of the transmission of impulses across the cerebral cortex made elsewhere (1934a) on the basis of Sherrington's *c.e.s.* As a matter of fact, if the recruitment and successive fractionated discharge of the various groups of cortical neurons had to be described entirely in terms of the internuncial bombardment responsible for it, the diagrams, owing to the very large number of neurons to be considered, would lose their didactic value.

However, there are cases in which the concept of *c.e.s.* as an enduring state of excitation of single cells cannot be used, not even to simplify theoretical arguments, as for example, when the simultaneity of arrival of two volleys of impulses is the necessary condition for threshold stimulation (cf. later discussion of inhibition), or when the response of the neuron depends more on

the spatial distribution of the active synapses than on the total number of impulses (1938c).

(b) *The multiple chains of internuncial cells* (*M*, Fig. 2) *as elementary units of transmission.* The question so often mentioned in the literature, as to whether a two-neuron (one synapse) arc sets up motor responses, can now be satisfactorily answered. Since the temporal summation of impulses arriving in succession through the same synapse is hardly possible, there can be no doubt that some cells in the nervous system are stimulated above threshold when a sufficiently strong synchronous volley of impulses through a homogeneous path is delivered to them. Obviously the cells with one-to-one transmission are those having either large synapses with individual fibers, or those having large sections of their soma covered by synapses of fibers from one homogeneous pathway (1933b). The rest of the neurons will fire only when impulses arrive simultaneously through several different pathways.

In the spinal cord it can be established (1938c) that the motoneurons have synapses of heterogeneous origin, so that conduction of impulses through a single pathway cannot result in the activation of all the synapses in any discrete zone of the soma, while many internuncials, especially in Cajal's intermediate nucleus and in the posterior horn, have homogeneous synapses. These cells must fire when a sufficiently large synchronous volley of impulses enters into the cord through the posterior roots; and in fact they do so, because (1) subliminal stimuli cause facilitation, and (2) internuncial potentials precede motor discharge and are obtained at a lower strength of stimulation (Gasser and Graham, 1933; Hughes and Gasser, 1934a, b).

When anatomical conditions prevent the convergence of impulses and therefore make it impossible for a two-neuron arc, such as that formed by fiber *f* and the motoneuron of Fig. 3, to transmit impulses, the additional activity of one internuncial neuron (i_1, Fig. 3) may result in transmission. If the first impulse through fiber *f* fires cells i_1, the motoneurons will respond to a second *f* impulse arriving simultaneously with the i_1 impulses, but obviously a transmission unit containing only one internuncial neuron cannot transmit impulses at a frequency below 1000 impulses per second. Increase in the number of links in the internuncial chains diminishes the frequency, and yet in the case of the oculomotor preparation, the frequency of shocks delivered to the posterior longitudinal bundle and adjacent pathways must be rather high, *i.e.*, 100 per sec. (Figs. 6 and 9.) Transmission of impulses at lower frequency demands the activation of much more complex chains of neurons, which are found only in the so-called primary nuclei of the sensory nerves—the posterior horn of the spinal cord, etc. The urgent need for including in physiological diagrams these nuclei, which form the most complex part of the medulla and cord, is herewith emphasized.

The concepts of the two-neuron arc, or of an arc with a fixed number of internuncials, lose their physiological meaning. On the one hand the impulses may set up responses of the motoneurons after having crossed a variable num-

ber of synapses, depending upon the state of the centers; and on the other hand, the internuncials are not intercalated between afferent fibers and effector cells. They form collateral chains superimposed upon the shortest path which, if a sufficient background of facilitation exists, is undoubtedly passable.

(c) *Fractionation of the internuncial and motor pools into active and inactive groups.* The elementary phenomenon responsible for fractionation consists in this, that threshold stimulation of a neuron is obtained only by summation of impulses delivered at several synapses. Of the neurons reached by the fibers of the active tracts only those respond upon which convergence of impulses takes place; the other neurons remain in the subliminal fringe (Sherrington, 1931). However, since each internuncial axon branches out and establishes connections with a large number of other internuncial neurons, it is difficult to understand how during continued stimulation the impulses may fail to spread into neighboring channels and engage a progressively increasing number of neurons producing avalanche conduction (Cajal, 1909; Herrick, 1926).

The fractionation of the neurons of a pool into active and inactive groups is found not only in reflex physiology, but is a general feature of the activity of the nervous system. A most demonstrative example is the recent observation of Marshall, Woolsey and Bard (1937; cf. Bard, 1938) on the physiological projection of the surface of the body onto the sensory cortical areas. Despite the many possible channels for the dispersion of impulses, only a discrete portion of the cortex becomes active. This indicates that here, as in the case of the retinal projection, the fractionation is successively maintained in each internuncial station (cf. 1934b, Fig. 36).

One of the most remarkable features of fractionation is that, once established, it continues in the absence of peripheral stimulation. For example, stimulation of a single semicircular canal results in a response of the motor apparatus of the eye producing nystagmus with a component, the "nucleus," invariable for each canal and another component, the "appendage," which may be reversed by concurrent stimulation of another canal (1933e) or even by stimulation of static receptors (1931). The interesting fact is that if the appendage of a response has been reversed by the concurrent stimulation of another canal, the reversal is maintained after concurrent stimulation stops. Likewise, the appendage of a response may be reversed by the after-discharge of a previous stimulation. This indicates that certain labyrinthine impulses may enter into two different channels, but once they have entered one of them they do not leave it during the remainder of the response. Even more, they force other impulses to use the same channel, with the result that they summate; and two stimuli in isolation apparently antagonistic, when delivered simultaneously give rise to a stronger response.

How the reversal is initiated it is not difficult to understand. In Fig. 12, f_1, f_2, and f_3 are fibers of the vestibular nerve and it is assumed that two synapses must be activated in order to insure the passage of the impulse across the synapse. It is clear that stimulation of fiber f_2 will always fire cell N, setting up the nucleus of the response and that concurrent stimulation of

fibers f_1 and f_2 will cause response of cell *1*, setting up the appendage A_1, while concurrent stimulation of f_2 and f_3 must set up appendage A_2.

Now it is known (1933c, Figs. 4 and 8) that the pools of neurons of the reticular formation send numerous recurrent (centrifugal) fibers back to the primary nuclei, thus forming a closed chain of type *C* (Figs. 2 and 12); and

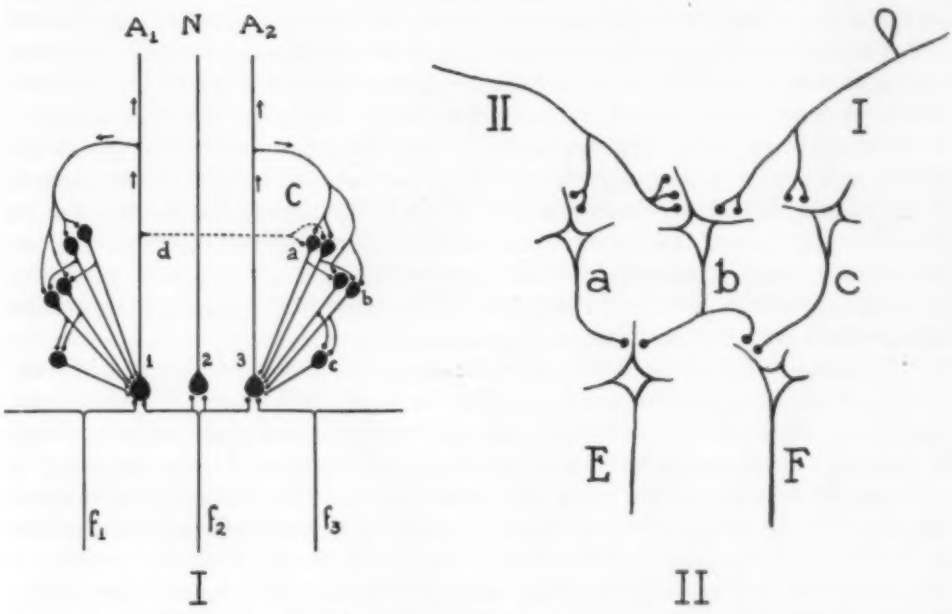


FIG. 12. I. Diagram explaining the production of reflex reversal by concurrent stimulation of two fibers (f_1 and f_2 *or* f_2 and f_3) from different peripheral sense organs and its maintenance by the impulses conducted by closed chain *C*, after fiber f_3, which initiated the response of cell *3*, ceases conducting. Each one of the links in the closed chain represents a multiple chain of neurons (*M*, Fig. 2) such as is illustrated in the diagram of Fig. 3. Collateral *d* by lowering the threshold of cell *a* and thus causing two impulses to cross through cell *3* in quick succession may produce inhibition, for cell *3* will acquire a high subnormal threshold.

II. Diagram of Gasser (1937c) explaining reciprocal innervation. It is assumed that threshold stimulation of neurons with normal threshold requires simultaneous activation of two synaptic knobs, but three knobs are required to stimulate a neuron having subnormal threshold. When fiber I conducts a rhythmic series of impulses at low frequency neuron *F* is stimulated by the *b* and *c* impulses and the flexor muscle contracts, but if fiber II then becomes active, cell *b* will be forced to discharge an extra impulse and to acquire subnormal threshold. Henceforth cell *b* will be able to respond only to the impulses conducted by fiber II, the result being that the extensor muscle contracts, while the flexor muscle relaxes because the *b* and *c* impulses reach neuron *F* at intervals longer than the period of effective summation of impulses delivered at neighboring synapses.

it is also known (1928, 1931, 1933) that lesions in the reticular substance, destroying among others those recurrent pathways, modify the transmission of impulses through the primary nuclei. The assumption lies therefore at hand that when the f_3 fiber stops conducting, the impulses brought back to the vestibular nuclei through the *C* chain maintain the state of facilitation of cell

3 and raise to threshold value the stimulating effect of the f_2 impulses, which continue setting up the appendage A_2 as if the f_3 impulses were still being delivered.

In systems having an extensive anatomical distribution such as the internuncial nuclei in the medulla and pons or in the spinal cord, analysis of the individual closed chains of neurons cannot be made, but in other organs, such as the cerebral cortex, the study may be carried out much farther. It is found (1934a, 1938d) that the arrangement of afferent fibers and cortical dendrites and axons in closed chains is such that the successive volleys of internuncial impulses must be delivered again and again in great density to the cells—internuncials and effectors—reached by the afferent volley, while the neighboring cells, which receive only small and infrequent volleys, must remain in the subliminal fringe. Thus it must be concluded that in the cerebral cortex the arrangement of the internuncial cells in closed chains, which force the impulses to use the same pathways repeatedly, is an anatomical mechanism leading to fractionation; and there is evidence to show that the same mechanism is operative also in subcortical centers.

(d) *Long-lasting facilitation, after-discharge.* At present it is generally believed (cf. 1935c; Eccles, 1936b, p. 394; Fulton, 1938 Chap. IV) that long-lasting facilitation and after-discharge are maintained by internuncial bombardment. The bombardments of relatively short duration can be satisfactorily explained by open chains of neurons having a few links. As a rule (cf. Kemp, Coppée and Robinson, 1937) it may be calculated that the passage of impulses through each internuncial station in the medulla and midbrain demands 1 msec. or slightly more (synaptic delay plus conduction time). Consequently, open internuncial chains such as are illustrated in Fig. 3 will be able to maintain facilitation and after-discharge for 4 msec. But long-lasting bombardment necessarily demands repeated passage of the impulses through the same internuncial cell (Bremer and Rijlant, 1926; Forbes, Davis, and Lambert, 1930). The internuncial chains through which the impulses circulate have been called reverberating circuits (Ranson and Hinsey, 1930) and closed self-reexciting chains (1933c).

Since the summation of subnormality progresses but slowly at low frequencies, a closed chain having a large number of links can remain in activity for considerable periods of time; but short chains, in which the impulses circulate at high frequency, must have a short time constant, because the passage of only a few impulses will create a high threshold and stop conduction. Inhibition must then result (1936). For example, in the diagram of Fig. 12 impulses may circulate through the closed chain *C* at different rates. If the circuit should be closed through cells *a* the rate would be high, because the impulse initiated in cell *3* would return in about one msec. to the same cell after crossing cells *a;* but if the cell *3* impulse should fail to reach the threshold of cells *a* and return through *b*, the rate would be lower. With a long chain, *i.e.*, one with many internuncials in series, or a chain including long fiber paths, the rate of circulation may be low enough to allow activity for considerable

periods of time, especially when fiber f_2 or f_3 also is conducting a series of impulses. However, if while chain *C* is working at low frequency, facilitation of cells *a* by impulses through collateral *d* should force the impulse from *3* to cross these cells and to restimulate cell *3*, the activity must cease, because two discharges at the rate of 1000 per second create in cell *3* so high a threshold that further transmission through this cell is blocked.

Thus, the activity of closed chains of internuncial neurons leads, under certain conditions, to facilitation, and under other conditions to inhibition. For this reason it seems best to drop the qualifications "reverberating" and "self-reexciting," which have too strict a meaning. The function of the closed chains of neurons must be analyzed in each particular case, as it must be determined by experiment whether a certain system of closed chains may become rhythmically active in the absence of peripheral stimulation or of impulses arriving from other centers.

There is evidence that in the case of the internuncial system regulating the discharge of ocular motoneurons, the closed chains of neurons in the reticular formation and vestibular nuclei are dependent for the initiation and maintenance of their activity on the constant stream of impulses set up in static receptors such as the labyrinth, the proprioceptors of the neck muscles, etc., so that even when by suitable operation the closed chains are made short, their activity may continue for long periods of time. This point deserves detailed consideration, for it leads to the problem of the nature of after-discharge. Is after-discharge the continuation of a newly created activity, or is it simply a particular case of reflex reversal which maintains the impulses, ordinarily passing through certain channels, in another set of channels?

It has been shown (1928, 1933c, p. 22) that vestibular after-discharge may be enormously prolonged by destroying parts of the reticular formation. The neurons left after the operation still formed closed loops (1933c, Fig. 8) but evidently short ones. With the now available knowledge of the recovery cycle of motoneurons, if an attempt is made to explain the after-discharge in terms of autochthonous activity of the closed circuits, the result becomes paradoxical. The destruction of internuncial cells shortens the chains and favors the creation of a high, subnormal threshold, because in order to maintain the internuncial bombardment, the remaining neurons must discharge at high frequency; nevertheless, the after-discharge is prolonged. The explanation is prompted by diagram I of Fig. 12, which indicates that if impulses started somewhere else are fed into them, the closed chains do not need to maintain circulation of impulses at the high frequency which autochthonous activity would demand. Fiber f_2 now represents one of the fibers from static labyrinthine receptors which set up the tonus of the external rectus eye muscle by firing the few motoneurons reached by the axon of cell *N*. The intercurrent stimulation of fiber f_3 brought in the motoneurons innervated by A_2, and the contraction of the muscle increased. When the stimulus of fiber f_3 was withdrawn, the impulses conducted back to the primary nuclei through the *C* chain maintained facilitation of cell *3* and the f_2 impulses were still capable

of crossing that synapse, with the result that muscle remained contracted (after-discharge) until subnormality was created in some neuron of the *C* chain. If the bombardment of cell *3* by the *C* chain (cells *a*, *b* and *c*) is mild, the f_2 impulses will set up discharges of cell *3* at low frequency; but under ordinary conditions, when the *C* chains are complete, many synapses of the *3* cells are simultaneously activated and the impulses are forced to circulate at higher frequency. The result is that subnormality is more rapidly created and after-discharge stops earlier.

In how far this argument applies to the spinal cord cannot be determined without direct experiments. It is likely, however, that the argument has general application, for the reason that long-lasting after-discharge hardly ever appears without a background of tonic activity (decerebrate rigidity, etc.), which obviously is due to a continuous stream of impulses arriving either from the periphery or from other centers.

(e) *Rhythmic reflexes.* Stimulation of the semicircular canals results in a rhythmic reflex, nystagmus, characterized by a succession of contractions and relaxations of the eye muscles. The records of the action potentials of the eye muscles or of their motor nerves during nystagmus are similar to the records in Figs. 10 and 11, the similarity being enhanced by the fact that the grouped discharges in Figs. 10 and 11 were obtained during continuous stimulation in the same way as nystagmus is produced in the presence of a continuous stream of labyrinthine impulses. Both sets of phenomena seem to have the same explanation.

In the classical theory of the production of rhythmic reflexes (Graham Brown, 1914; Forbes, 1922; Spiegel, 1929) the attempt was made to explain simultaneously reciprocal innervation and rhythm on the basis of a succession of states of activity and rest, as due to the fatigue of certain cells. This explanation is consistent with present knowledge, although rhythm and reciprocal innervation must be accounted for separately. Rhythm is generally accompanied by reciprocal innervation but it may appear without it, even when the antagonistic muscles contract and relax simultaneously. The following discussion, therefore, refers to a frequent form of nystagmus which is perhaps the fundamental one, in which the agonist muscle shows a succession of slow contractions and quick relaxations of short duration, while the antagonist muscle shows only quick contractions (Fig. 13, II; cf. 1935f).

A number of significant facts are known: (1) During the slow phase of nystagmus the contraction of the agonist is due to an increase of the number of active motor units and to an increase in the frequency of their discharge. The speed of the contraction, *i.e.*, the speed of the recruitment of the motor units, is directly proportional to the strength of the stimulus, while the duration of the contraction is inversely proportional to it. Many things seem to indicate that the onset of the quick phase is caused by a trigger-like mechanism, which becomes active when the contraction has reached a certain level dependent upon the strength of the stimulus. (2) The relaxation of the agonist and the contraction of the antagonist during the quick phase are very fast,

i.e., the recruitment of the motor units of the antagonist proceeds rapidly, the discharge of the motoneurons taking place with a great deal of synchronism. The duration of the quick component varies between narrow limits (McCouch and Adler, 1931) from 100 msec. in weak nystagmus to 80 msec. in strong

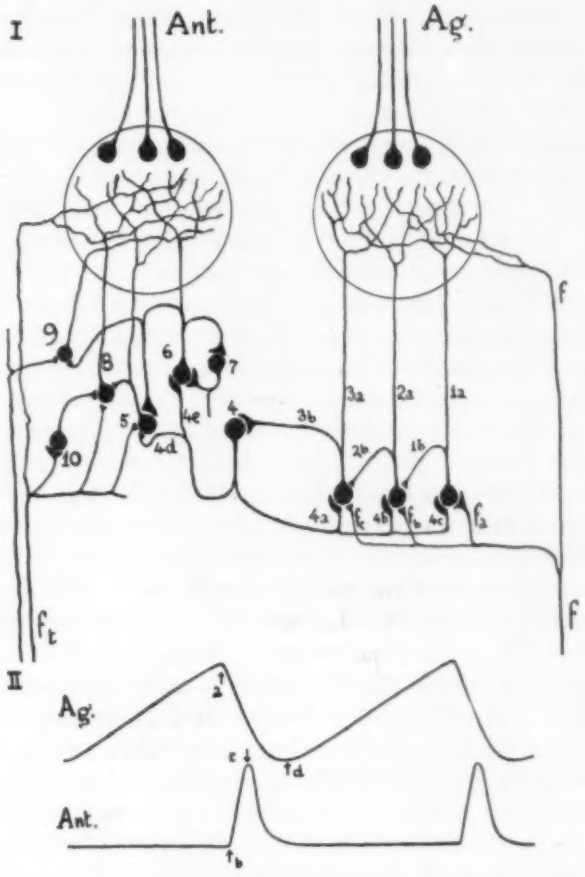


FIG. 13. I. Diagram explaining the production of rhythm during vestibular nystagmus. Fiber *f* is supposed to carry the continuous series of impulses started at the cristae of the semicircular canals which set up the nystagmus. Fibers f_t are supposed to be maintaining the tonus of the antagonistic muscle; *1*a, *1*b, *2*a, *2*b, *3*a, *3*b are branches of the axons of cells *1*, *2* and *3*, *4*a, *4*b, *4*d, *4*e are branches of the axon of cell *4*; f_a, f_b, f_c are branches of fiber *f*.

II. Diagram of the rhythmic succession of contractions and relaxations of the antagonistic muscles during the nystagmus explained by diagram I. Rising of the line indicates contraction. The interval between turning points *a* and *b* is never less than 3 to 4 msec.; the interval between turning points *c* and *d* may be 50 msec. long.

nystagmus (1935f). (3) The stream of impulses created in the vestibular nuclei is a constant one. The interrupted discharge of the motoneurons is attributable to the activity of neurons located in the reticular formation. In fact, if part of the reticular formation or of its pathways is destroyed, the nystagmus is converted into a monophasic reflex, the agonist remaining contracted as long as the peripheral stimulus lasts (1933c). (4) The relaxation of the agonist is not attributable to an active inhibitory process but only to a lack of excitatory impulses (1933d). (5) The turning points in the antagonistic muscles are not synchronous (1935f) (Fig. 13, II).

In view of these facts it is not difficult to construct a diagram explaining the production of rhythm. In Fig. 13, *f* represents the fibers of the semicircular canals which, after interruption in the primary vestibular nuclei, reach the motor pool of the agonist and the internuncial pool (cells *1*, *2*, *3*). In order to simplify the diagram, only a few internuncial cells have been included and it must be assumed, therefore, that, although successive impulses through the same synapse never summate, the period of summation of impulses arriving through different synapses is of long duration. This is identical with making the linkage between neurons through chains of type *M*, as in Fig 3. Cells *4* and *5* to *9* also belong to the internuncial system, and fibers f_t represent those from static receptors such as the labyrinth and proprioceptors of the neck, which maintain the tonus of the antagonist. The effectiveness of stimulation is indicated by the size of the synaptic knobs. It is assumed that the synapses formed by a large terminal knob, representing a number of simultaneously active ordinary knobs, are one-to-one synapses, while those formed by small knobs demand summation of the effects at two adjacent knobs in order to fire the underlying neuron.

When fiber *f* starts to conduct, its rhythmic series of impulses successively recruits internuncial and motoneurons: the first *f* impulse does not set up any response of motoneurons, neither does it fire cells *2* and *3*, but it fires cell *1;* the second *f* impulse summates with the impulses delivered by the branches of *1* and fires some motoneurons and cells *1* and *2;* the third *f* impulse summates with the impulses of *1* and *2* and fires a larger number of motoneurons and cell *3*. The fact that cell *3* responds means that after completion of its synaptic delay cell *4* also fires and consequently cells *1*, *2*, and *3* must fire again. For this reason the fourth *f* impulse finds the motor nucleus in a greater state of facilitation, as it has just received two impulses from each internuncial cell and is capable of setting up a response of a large number of motoneurons. The contraction of the muscle is then strong; but, a relaxation must immediately follow because the discharge of two impulses by cells *1*, *2*, and *3* in quick succession, at an interval of about 1.2 msec., which is equal to the synaptic delay at *4* plus the synaptic delay at *3*, *2*, or *1*, has created in them a strong subnormality, so that the *f* impulses cannot reach their threshold. Consequently since no internuncial impulses are produced, the facilitation of the motor nucleus ceases and the following *f* impulses alone fail to set up a response of the motoneurons. As long as the subnormal state of neurons *1*, *2*,

and *3* lasts, *i.e.*, no more than 100 msec., the muscle remains relaxed, but as soon as recovery has been completed the same process is started once more; internuncials and motoneurons are successively recruited* and the contraction of the muscle increases until the discharge of *4* again creates a state of subnormality in *1*, *2*, and *3*. Evidently if by means of suitable lesions the connections of cell *4* with cells *1*, *2*, and *3* are severed, a sudden development of subnormality becomes impossible and the muscle will remain contracted as long as the *f* impulses are being produced.

The contraction of the antagonist is explained by the existence of branches *4d* and *4e* of the axon of cell *4*. When this cell fires it not only causes the relaxation of the agonist, but also produces a contraction of the antagonist, for it sets into activity chains of neurons *5-6-7* which on the one hand deliver volleys of impulses to the antagonistic pool and on the other hand lower the threshold of cells *8* and *9*, thus increasing the transmission of the tonic (f_t) impulses to the motor pool. The antagonistic muscle contracts rapidly, but it must relax again very soon because the impulses cross through the short chains formed by cells *5* to *9* at high frequency and the rapidly created subnormality prevents further conduction of impulses to the motoneurons.

There is extensive experimental evidence to show that neurons *4* to *8* are located at least in part in the reticular substance in the pons. Moreover, it was found possible to place lesions in the vestibular system allowing those groups of neurons to become rhythmically active in the absence of stimulation of the semicircular canals (1928, p. 90; 1933c, p. 29). The eye muscles showed then a peculiar form of nystagmus; the antagonistic muscles underwent a rhythmic succession of fast and short-lasting simultaneous contractions, separated by longer phases of relaxation. Stimulation of the labyrinth did not produce any other result than increase of the frequency of the contractions; but when an additional part of the reticular substance was destroyed, the spontaneous nystagmus ceased and the labyrinth was again able to produce either a monophasic reflex consisting of a steady contraction of the agonist, or even a rhythmic nystagmus in which the contraction of the agonist was partially checked by small quick relaxations.

The relaxation of the agonist begins earlier than the contraction of the antagonist, because the discharge of cell *4*, which makes cells *1*, *2*, and *3* subnormal, does not result in contraction of the antagonist until after some recruitment has taken place in chains *5* to *7*. The interval between the beginning of relaxation of the agonist and the start of contraction of the antagonist is smaller the stronger the nystagmus, but even in the case of a strong reflex the difference is not less than 3 to 4 msec., indicating that the transmission of impulses from cell *4* to the antagonist pool takes place through at least three or four internuncial neurons.

After its relaxation the agonist again begins to contract when cells *1*, *2*,

* It should be noted that the period of relaxation of the agonist is made up of two parts: (1) the time during which the transmission of impulses is blocked; and (2) the time necessary for the recruitment of internuncial neurons.

and *3* recover from subnormality, while the contraction of the antagonist ceases when cells *5* to *7* become subnormal. Since the creation of subnormality demands less time than recovery from subnormality, it is to be expected that the contraction of the antagonist should be briefer than the relaxation of the agonist. In fact differences as great as 50 msec. have been found.

Despite its simplicity, the diagram in Fig. 13 explains why the rhythm may be profoundly modified by intercurrent stimuli. The rate of recuitment of neurons *1* to *4* and of neurons *5* to *9* depends not only upon the impulses conducted by fibers *f*, but also upon the impulses conducted by all the other fibers having connections with the internuncial cells; and the amount of subnormality necessary to block conduction of impulses also depends upon the amount of pre-existent internuncial activity.

Although the available information, especially the anatomical data, is not sufficient to warrant the application of the diagram given in Fig. 13 to other rhythmic activities of the nervous system, it seems likely that some of the elementary phenomena are in every case essentially the same (cf. Sherrington, 1906; Wachholder, 1924; Bronk and Ferguson, 1935) and that other rhythmic reflexes differ from nystagmus only in the rates of recruitment of the motor units during the alternating phases.

(f) *Inhibition, reciprocal innervation.* At present it is generally believed (cf. Eccles, 1936b; Beritoff, 1937; Fulton, 1938; Lorente de Nó, 1936) that specific inhibitory impulses, even if there were specific inhibitory fibers (Kato, 1934), do not exist. Inhibition must, therefore, be explained in terms of processes created by the same impulses that create excitation. The problem of inhibition has been submitted to careful analysis by Gasser (1935b; 1937a, b, c,; 1938) who has suggested several diagrams accounting for different types of the phenomenon. Two elementary processes are considered: (1) rise in threshold of the neurons due to summation of subnormality; 2) lowering of the stimulating value of a synchronous volley of impulses by its fractionation into two volleys delivered at an interval longer than the effective period of summation of impulses arriving at different synapses.

Since the motoneurons and presumably all other neurons work at threshold, there is no doubt that either of the two processes will cause a deficit of response (inhibition). Several instances have been mentioned in this article as well as in previous papers, in which it was necessary to attribute the absence of response of ocular motoneurons to reduction or cessation of internuncial activity (Fig. 7, *13* to *22*); and the diagrams in Figs. 12, I, and 13 explain how a closed chain of neurons including only a few links may act as an inhibitory mechanism. Summation of subnormality, however, will lead to the production of rhythm (Figs. 10 and 11) rather than to sustained inhibition, unless it is produced and maintained in cells which are common links of antagonistic chains of neurons.

The diagram suggested by Gasser (1938c) which is reproduced in Fig. 12, II, includes a link of this type in cell *b;* subnormality of that cell will allow activation of cell *E* or cell *F*, but not a simultaneous activation of both.

A similar linkage between paths A_1 and A_2 (Fig. 12, I) would explain the reciprocal exclusion of the appendages of vestibular nystagmus, and the same type of linkage between fibers f and f_t (Fig. 13) would explain the initial relaxation of the antagonist, which accompanies the initial contraction of the agonist in certain forms of nystagmus. The existence of an additional linkage ensuring reciprocal innervation is likely, because as previously mentioned, destruction of certain internuncial nuclei may abolish reciprocal innervation and cause co-contraction without abolishing rhythm.

Inhibition through the subnormality of cell *b* (Fig. 12, II) is very different from inhibition produced by a Wedensky block (Lucas, 1917, Fig. 22). Under certain conditions increase in the frequency of a train of impulses in nerve establishes the Wedensky block; and once established, the block is impassable for any impulse.* Subnormality, on the contrary, produces a block for weak stimuli only, and no matter how strong the subnormality may be, it will be "broken through" if the stimulus is strengthened (Fig. 10, *15*).

In principle, then, the problem of inhibition does not offer insurmountable obstacles, and the fact that it is due to excitation of certain neurons explains the similarity found by Sherrington (1925) and by Eccles and Sherrington (1931c) between *c.e.s.* and *c.i.s.* Inhibition must have all the properties of excitation, *i.e.*, recruitment, subliminal fringe, etc., the only difference being that inhibition does not set up motor responses. Furthermore, inhibition must be maintained chiefly by internuncial bombardment, but other factors (cf. Dusser de Barenne and McCulloch, 1937; Dusser de Barenne, McCulloch, and Nims, 1937; Gerard, 1936a) may also become operative under given conditions.

The difficulties in the explanation of reciprocal inhibition appear when an attempt is made to identify the anatomical mechanisms, because inhibition by fractionation of synchronous volleys of impulses arriving at different synapses demands that excitation of some cells be brought about through pathways insuring a perfect synchronism of the arrival of impulses, despite the causes for the temporal dispersions responsible for the statistically constant bombardment observed during facilitation (cf. above, sub *a*). The timing of the arrival of the impulses to the neurons responsible for inhibition must indeed be accurate. Fig. 14 reproduces records of an experiment in which the stimulating value of a synchronous volley of impulses was reduced by dividing it into two volleys delivered at variable intervals.

The diagram at the top explains the conditions of the experiment (cf. 1935c, Fig. 2). An F shock (F_t) capable of firing fibers f_1 and f_2 (records *1*, *5*, *7*) or f_1, f_2, and f_3 (*9*) was preceded by a smaller F shock (F_c) capable of firing only fiber f_1 (record *4*). The conditioning shock was weak so that the f_c volley was not perfectly synchronous, which caused an apparent increase of the duration of the period of summation of the impulses delivered at neighboring synapses (cf. records *6* and *7*). Nevertheless, there was an interval between

* Several convincing reasons why a Wedensky block cannot be considered as the elementary mechanism underlying inhibition were given by Fulton (1926).

shocks (records *3* and *10*) during which the response to F_t was clearly diminished. This interval was short, because the bombardment through internuncial cells i_1 started by shock F_c caused the arrival to the motor nucleus of impulses which summated with the F_t impulses and gave rise to a facilitated response (records *2* and *8*).

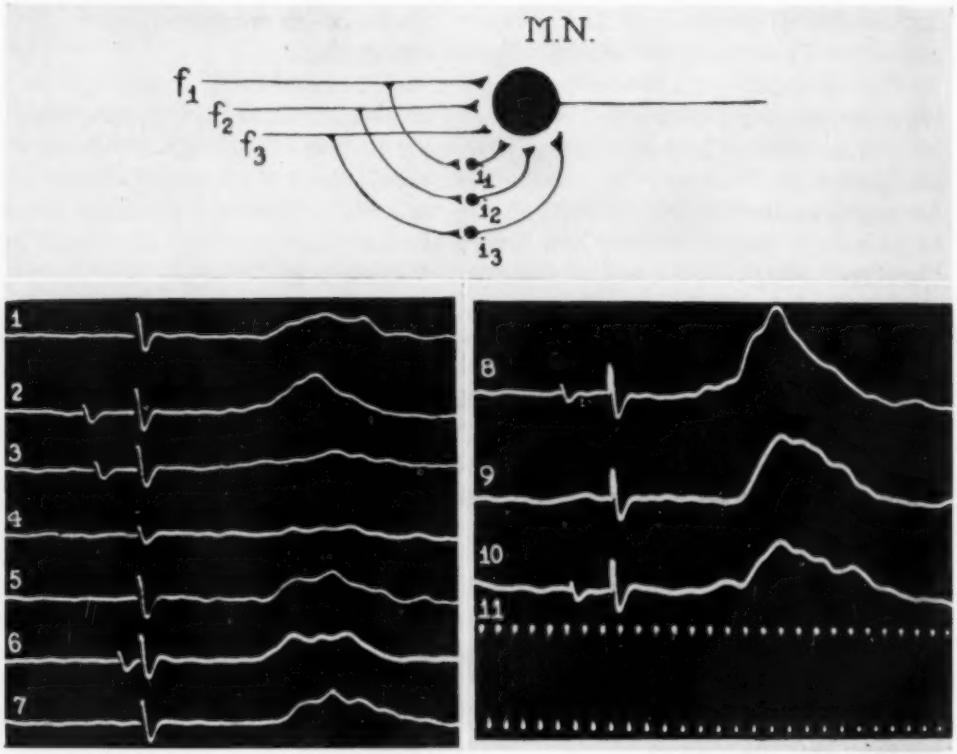


FIG. 14. Oculomotor preparation; responses recorded from the trochlear nerve (6-20-37). Stimulating electrodes on the floor of the fourth ventricle. The conditioning shock had the same strength in both series of records. The response to it in isolation is shown in record *4*. The testing shock was 220 per cent stronger than the conditioning shock in records *1* to *7*, and 300 per cent stronger in records *8* to *10*. *1*, *5*, *7* and *9*, responses to the testing shock in isolation. Note that in records *2* and *8* the response to the testing shock is facilitated; it is depressed in records *3* and *10* but is unaltered in record *6*. *11*, timing film (5000 cycles per second).

The existence of synchronizing mechanisms has been mentioned in previous paragraphs (p. 226). It is, however, not improbable that future research will lead to the discovery of still other, as yet unknown, synchronizing factors and of other agencies capable of maintaining inhibition.* Synchronization of

* Observations made on peripheral nerve (1938a) suggest that subliminal stimulation may play a role in the maintenance of inhibition. When a train of subliminal shocks is delivered to a nerve, each shock is followed by a period of local summation and a period of postcathodal depression, but the duration of the period of summation diminishes with each successive shock of the train, at the same time that the depth of the postcathodal

a large number of elements is a prominent characteristic of the activity of the cerebral cortex (cf. Bishop and O'Leary, 1936; Bishop, 1936). Gerard (1935a, b) has made a thorough analysis of the various factors, which in addition to the play of nerve impulses on neurons may be operative in modifying cortical rhythms. They belong into the class of enduring changes and therefore lie beyond the scope of the present paper (cf. above, parag. *a*).

Summary

An attempt is made to correlate data on the anatomy of the central nervous system with the results of physiological experiments.

The nervous system is composed of an exceedingly large number of interlacing pathways, which offer numerous opportunities for the conduction of impulses into divergent paths; but during activity it becomes fractionated into a group of active and another group of inactive neurons. The active neurons are arranged in convergent chains of relatively simple composition, which may be called the multiple (*M*, Fig. 2) and the closed chain (*C*, Fig. 2) through which impulses circulate. The fractionation is attributable to the fact that stimulation of a neuron requires the activation within a short period of time, which for the motoneurons is less than 0.3 msec., of several synapses having a determined spatial distribution on the neuron. The rigidity of the conditions necessary for the effective summation of impulses delivered to synaptic junctions is such that the impulses circulating through the active chains, despite their being very numerous, remain subliminal for the neurons of the inactive group.

Impulses circulating through the chains of neurons of the internuncial system create a statistically constant stimulus of motoneurons and internuncials, as both classes of neurons are submitted to a constant bombardment by impulses being delivered at their synapses. The neurons respond rhythmically at a rate dependent upon the strength of the bombardment and the rate of their recovery.

The multiple chain of neurons (*M*, Fig. 2) is the elementary unit of transmission; it supersedes the classical reflex arc with a fixed number of synapses. The rate at which a multiple chain may transmit impulses depends upon the number of neurons it contains; the greater the number of links, the lower being the minimal rate.

The closed chain of neurons (*C*, Fig. 2) may play different roles according to the number of links that it contains. If the number is small, activation of the chain may result in inhibition, but if the number of links is large enough it may result in sustained facilitation or discharge. It is indicated that after-discharge does not necessarily require autochthonous activity of closed chains of neurons; after-discharge must rather be interpreted as an especial

depression increases. If these phenomena should take place during synaptic transmission, subliminal stimulation would maintain the high subnormal threshold in the periods between discharges. The neurons would then be accessible only to strong stimuli constituted by the absolutely synchronous arrival of several impulses.

case of reflex reversal, maintained by closed chains of neurons which keep the constant stream of impulses that have arrived from the periphery or from other centers within channels opened by the intercurrent stimulation.

The participation of the internuncial system in the establishment of reflex reactions is explained in some detail on the basis of diagrams designed to account for the production of vestibular nystagmus.

The elementary mechanisms underlying inhibition are discussed.

REFERENCES

ADRIAN, E. D., and BRONK, D. W. The discharge of impulses in motor nerve fibres. Part I. Impulses in single fibres of the phrenic nerve. *J. Physiol.*, 1928, *66:* 81–101.
Part II. The frequency of discharge in reflex and voluntary contractions. 1929, *J. Physiol.*, *67:* 119–151.

BARD, P. Studies on the cortical representation of somatic sensibility. *Harvey Lectures*, 1937–38. (In press.)

BISHOP, G. H. The interpretation of cortical potentials. *Cold Spr. Harb. Symp. Quant. Biol.*, 1936, *4:* 305–317.

BISHOP, G. H., and O'LEARY, J. Components of the electrical response of the optic cortex of the rabbit. *Amer. J. Physiol.*, 1936, *117:* 292–308.

BERITOFF, J. Excitation and inhibition in the central nervous system regarded from the point of view of its neuron-neuropil structure. *Trans. J. Beritashvili Physiol. Inst.*, 1937, *3:* 21–86.

BREMER, F. Contribution à l'étude du problème de la transmission neuro-musculaire. *Arch. int. Pharmacodyn.*, 1930, *38:* 300–324.

BREMER, F., and HOMES, G. Une théorie de la sommation d'influx nerveux. *Arch. int. Physiol.*, 1932, *45:* 39–64.

BREMER, F., and KLEYNTJENS, F. Nouvelles recherches sur le phénomène de la sommation d'influx nerveux. *Arch. int. Physiol.* 1937, *45:* 382–414.

BREMER, F., and MOLDAVER, J. Etude pharmacologique de la courbe de sommation centrale chez la grenouille spinale. *C. R. Soc. Biol., Paris*, 1933, *112:* 727–730.

BREMER, F., and RYLANT, P. Recherches sur le mecanisme de l'action de la strychnine sur le système nerveux central. II. Etude des modifications, par la strychnine, des électromyogrammes des réflexes du chat et de la grenouille. *Mém. cour. Acad. Méd. Belg.*, 1926, *22:* 1–42.

BRONK, D. W., and FERGUSON, L. K. The nervous control of intercostal respiration. *Amer. J. Physiol.*, 1935, *110:* 700–707.

CAJAL, S. R. *Histologie du système nerveux de l'homme et des vertébrés*. Paris, Maloine. Vol. I, 1909; Vol. II, 1911.

COOPER, S., DENNY-BROWN, D., and SHERRINGTON, C. S. Reflex fractionation of a muscle. *Proc. roy. Soc.*, 1926, *B100:* 448–462.

CREED, R. S., DENNY-BROWN, D., ECCLES, J. C., LIDDELL, E. G. T., and SHERRINGTON, C. S. *Reflex activity of the spinal cord*. Oxford, Clarendon Press. 1932.

DENNY-BROWN, D. E. On the nature of postural reflexes. *Proc. roy. Soc.*, 1929, *B104:* 252–301.

DENNY-BROWN, D. E., and SHERRINGTON, C. S. Subliminal fringe in spinal flexion. *J. Physiol.*, 1928, *66:* 175–180.

DUSSER DE BARENNE, J. G., and MCCULLOCH, W. S. Local stimulatory inactivation within the cerebral cortex, the factor for extinction. *Amer. J. Physiol.*, 1937, *118:* 510–524.

DUSSER DE BARENNE, J. G., MCCULLOCH, W. S., and NIMS, L. F. Functional activity and pH of the cerebral cortex. *J. cell. comp. Physiol.*, 1937, *10:* 277–289.

ECCLES, J. C. Studies on the flexor reflex. III. The central effects produced by an antidromic volley. *Proc. roy. Soc.*, 1931, *B107:* 557–585.

ECCLES, J. C. The action of preganglionic impulses on ganglion cells. *J. Physiol.*, 1936a, *87:* 81P–83P.

ECCLES, J. C. Synaptic and neuro-muscular transmission. *Ergebn. Physiol.*, 1936b, *38:* 339–444.

ECCLES, J. C. Synaptic and neuro-muscular transmission. *Physiol Rev.*, 1937a, *17:* 538–555.

ECCLES, J. C. The discharge of impulses from ganglion cells. *J. Physiol.*, 1937b, *91:* 1–22.

ECCLES, J. C., and SHERRINGTON, C. S. Studies on the flexor reflex. IV. After-discharge. *Proc. roy. Soc.*, 1931a, *B107:* 586–596.

ECCLES, J. C. and SHERRINGTON, C. S. Studies on the flexor reflex. V. General conclusions. *Proc. roy. Soc.*, 1931b, *107:* 597–605.

ECCLES, J. C., and SHERRINGTON, C. S. Studies on the flexor reflex. VI. Inhibition. *Proc. roy. Soc.*, 1931c, *B109:* 91–113.

FORBES, A. The interpretation of spinal reflexes in terms of present knowledge of nerve conduction. *Physiol. Rev.*, 1922, *2:* 361–414.

FORBES, A. The mechanism of reaction in MURCHISON. *A handbook of general experimental psychology.*, Worcester, Mass., Clark University Press, 1934. (See p. 155).

FORBES, A. Conduction in axon and synapse. *Cold Spr. Harb. Symp. Quant. Biol.*, 1936, *4:* 163–169.

FORBES, A., DAVIS, H., and LAMBERT, E. The conflict between excitatory and inhibitory effects in a spinal center. *Amer. J. Physiol.*, 1930, *95:* 142–173.

FULTON, J. F. *Muscular contraction and the reflex control of movement.* Baltimore, Williams and Wilkins. 1926.

FULTON, J. F. *Physiology of the nervous system.* New York, Oxford Univ. Press, 1938.

GASSER, H. S. Changes in nerve potentials produced by rapidly repeated stimuli and their relation to the responsiveness of nerve to stimulation. *Amer. J. Physiol.*, 1935a, *111:* 35–50.

GASSER, H. S. The changes produced in the injury discharge of nerve fibers during the period following a propagated disturbance. *J. Physiol.*, 1935b, *85:* 15P–17P.

GASSER, H. S. In ERLANGER, J. and GASSER, H. S., *Electrical signs of nervous activity.* Philadelphia, Univ. Penn. Press, 1937a, p. 170.

GASSER, H. S. The control of excitation in the nervous system. *Harvey Lectures*, 1937b, *32:* 169–193.

GASSER, H. S. Reciprocal innervation. *Volume jubilaire publicé en l'honneur du Prof. J. Demoor.* Liege. 1937c, pp. 212–218.

GASSER, H. S. Recruitment of nerve fibers. *Amer. J. Physiol.*, 1938, *121:* 193–202.

GASSER, H. S. and GRAHAM, H. T. Potentials produced in the spinal cord by stimulation of dorsal roots. *Amer. J. Physiol.*, 1933, *103:* 303–320.

GERARD, R. W. Factors controlling brain potentials. *Cold Spr. Harb. Symp. Quant. Biol.*, 1936a, *4:* 292–298.

GERARD, R. W. Factors influencing brain potentials. *Trans. Amer. neurol. Ass.*, 1936, pp. 55–57.

GRAHAM-BROWN, T. Die Reflexfunktionen des Zentralnervensystems mit besonderer Berücksichtigung der rhythmischen Tätigkeiten beim Säugetier. *Ergebn. Physiol.*, 1916, *15:* 480–790.

HERRICK, C. J. *An introduction to neurology.* 4th ed. Philadelphia, W. B. Saunders Co., 1927.

HUGHES, J., and GASSER, H. S. Some properties of the cord potentials evoked by a single afferent volley. *Amer. J. Physiol.*, 1934a, *108:* 295–306.

HUGHES, J., and GASSER, H. S. The response of the spinal cord to two afferent volleys. *Amer. J. Physiol.*, 1934b, *108:* 307–321.

KATO, G. *The microphysiology of nerve.* Tokyo, Maruzen, 1934.

KEMP, E. H., COPPÉE, G. E., and ROBINSON, E. H. Electrical responses of brain stem to unilateral auditory stimulation. *Amer. J. Physiol.*, 1937, *120:* 304–315.

KLEYNTJENS, F. Contribution à l'étude des effets d'excitations antidromiques sur l'activité réflexe de la grenouille spinale. II. Facilitation centrale par influx antidromiques. *Arch. int. Physiol.*, 1937, *45:* 444–453.

LORENTE DE NÓ, R. Etudes sur le cerveau postérieur. III. Sur les connexions extra-cérébelleuses des fascicules afférents au cervelet, et sur la fonction de cet organ. *Trab. Lab. Invest. Biol. Univ. Madrid*, 1924, *22:* 51–65.

LORENTE DE NÓ, R. *Die Labyrinthreflexe auf die Augenmuskeln nach einseitiger Labyrinthexstirpation nebst einer kurzen Angabe über den Nervenmechanismus der vestibularen Augenbewegungen.* Vienna, Urban and Schwarzenberg, 1928.

LORENTE DE NÓ, R. Ausgewählte Kapitel aus der vergleichenden Physiologie des Labyrinthes. Die Augenmuskelreflexe beim Kaninchen und ihre Grundlagen. *Ergebn. Physiol.*, 1931, *32:* 73–242.

LORENTE DE NÓ, R. Anatomy of the eighth nerve I. Central projection of nerve endings of internal ear. *Laryngoscope, St. Louis*, 1933a, *43:* 1–38.

LORENTE DE NÓ, R. Anatomy of eighth nerve. III General plan of structure of the primary cochlear nuclei. *Laryngoscope, St. Louis*, 1933b, *43:* 327–350.

LORENTE DE NÓ, R. Vestibulo-ocular reflex arc. *Arch. Neurol. Psychiat., Chicago*, 1933c, *30:* 245–291.

LORENTE DE NÓ, R. The interaction of the corneal reflex and vestibular nystagmus. *Amer. J. Physiol.*, 1933d, *103:* 704–711.

LORENTE DE NÓ, R. Reflex reversal and interaction of allied vestibular reflexes. *Amer. J. Physiol.*, 1933e, *105:* 122–134.

LORENTE DE NÓ, R. Studies on the structure of the cerebral cortex. I. The area entorhinalis. *J. Psychol. Neurol., Lpz.*, 1934a, *45:* 381–438.

LORENTE DE NÓ, R. II. Continuation of the study of the ammonic system. *J. Psychol. Neurol., Lpz.*, 1934b, *46:* 113–177.

LORENTE DE NÓ, R. The synaptic delay of motoneurons. *Amer. J. Physiol.*, 1935a, *111:* 272–282.

LORENTE DE NÓ, R. The effect of an antidromic impulse on the response of the motoneuron. *Amer. J. Physiol.*, 1935b, *112:* 595–609.

LORENTE DE NÓ, R. Facilitation of motoneurons. *Amer. J. Physiol.*, 1935c, *113:* 505–523.

LORENTE DE NÓ, R. The summation of impulses transmitted to the motoneurons through different synapses. *Amer. J. Physiol.*, 1935d, *113:* 524–528.

LORENTE DE NÓ, R. The electrical excitability of the motoneurons. *J. cell. comp. Physiol.*, 1935e, *7:* 47–71.

LORENTE DE NÓ, R. Observations on nystagmus. *Acta Oto-laryng.*, 1935f, *21:* 416–437.

LORENTE DE NÓ, R. Inhibition of motoneurons. In *The problems of nervous physiology and of behaviour. Jubileum Symposium, dedicated to Prof. J. S. Beritoff*. Tiflis, Georgia Branch Acad. Sci. U.S.S.R., 1936, pp. 231–247.

LORENTE DE NÓ, R. Subliminal stimulation of medullated frog nerve. *Amer. J. Physiol.*, 1938a. (In press).

LORENTE DE NÓ, R. Limits of variation of the synaptic delay of motoneurons. 1938b This Journal, *1:* 187–193.

LORENTE DE NÓ, R. Synaptic stimulation as a local process. 1938c. *J. Neurophysiol., 1:* 194–207.

LORENTE DE NÓ, R. The cerebral cortex. Chapt. XV in FULTON, J. F., *Physiology of the nervous system*. New York, Oxford Univ. Press, 1938d.

LORENTE DE NÓ, R. Responses of motoneurons and of motor axons to short induction shocks. *J. Neurophysiol.*, 1938e (to be published).

LORENTE DE NÓ, R., and GRAHAM, H. T. Recovery cycle of motoneurons. *Amer. J. Physiol.*, 1938 (to be published).

LUCAS, K. *The conduction of the nervous impulse*. Longmans, London, 1917.

MARSHALL, W. H., WOOLSEY, C. N., and BARD, P. Representation of tactile sensibility in the monkey's cortex as indicated by cortical potentials. *Amer. J. Physiol.*, 1937, *119:* 372–373.

MCCOUCH, G. P., and ADLER, F. H. Extraocular reflexes. *Amer J. Physiol.*, 1932, *100:* 78–88.

RANSON, S. W., and HINSEY, J. C. Reflexes in the hind limbs of cats after transection of the spinal cord at various levels. *Amer. J. Physiol.*, 1930, *94:* 471–495.

SHERRINGTON, C. S. *The integrative action of the nervous system*. New York, Scribner, 1906.

SHERRINGTON, C. S. Remarks on some aspects of reflex inhibition. *Proc. roy. Soc.*, 1925, *B97:* 519–545.

SHERRINGTON, C. S. Some functional problems attaching to convergence. *Proc. roy. Soc.*, 1929, *B105:* 332–362.

SHERRINGTON, C. S. Quantitative management of contraction in lowest level coordination. *Brain*, 1931, *54:* 1–28.

SHERRINGTON, C. S. Reflex inhibition as a factor in the coordination of muscular acts. *Rev. Soc. argent. Biol.*, 1934. (10 suppl.) 510–513.

SPIEGEL, E. A. Experimentalstudien am Nervensystem; der Mechanismus des labyrinthären Nystagmus. *Z. Hals-Nasen-u. Ohrenheilk.*, 1929, *25:* 200-217.

WACHHOLDER, K. Willkürliche Haltung und Bewegung insbesondere im Lichte elektrophysiologischer Untersuchungen. *Ergebn. Physiol.*, 1928, *26:* 568–775.

WHITAKER, J. G., and ALEXANDER, L. Die Verbindungen der Vestibulariskerne mit dem Mittel- und Zwischenhirn. Studien auf Grund experimenteller Verletzungen. *J. Psychol. Neurol., Lpz.*, 1932, *44:* 253–376.

LOCALIZATION OF CEREBRAL LESIONS BY ELECTRO-ENCEPHALOGRAPHY*

THEODORE J. CASE AND PAUL C. BUCY

From the Otho S. A. Sprague Memorial Institute and the Division of Psychiatry, and from the Division of Neurology and Neurosurgery, The University of Chicago

(Received April 11, 1938)

I. INTRODUCTION

A SURPRISINGLY high percentage of lesions of the cerebrum, particularly tumors, can be accurately localized by recording the alterations in the electro-encephalogram. Unlike the clinical manifestations of cerebral disease, the electrical changes which accompany lesions in the so-called "silent" areas are as definite and as localizable as those arising from lesions in any other portion of the cerebral cortex. The method is simple of application, once the apparatus is available, and examination does not require the attention or the active cooperation of the patient. Since it is not a tiring or painful experience, and since it in no way endangers the patient's life or disturbs his physical condition, the advantages of the method are obvious. The records, moreover, are graphic, objective and impersonal. Apart from these clinical advantages in diagnosis and localization of cerebral lesions the results are of sufficient general interest to invite the attention of neurophysiologists.

METHODS AND APPARATUS

The apparatus used consisted of three separate amplifying channels composed of resistance-capacity coupled amplifiers working into an ink writing oscillograph. The principal characteristics of the apparatus are: (1) Time constant of amplifiers 0.8 second; (2) Sensitivity as generally used such that 30 microvolts produces deflection of 1 mm. of inked line on moving tape; (3) Ink writer capable of recording any frequency from 0 to 170 cycles per sec. with slightly diminishing sensitivity above 100 cycles.

In operation all amplifiers are grounded together at one point and this point is attached routinely at the vertex, the grid leads of the several channels being attached by small silver plates about 1 cm. in diameter at any desired points on the cranium. When an area of interest is located, the central ground is shifted over or near this point and the grid leads grouped in radiating fashion about it at shorter distances from this center than before.

The deflection of the writing arm represents, then, the total voltage between the center of the system (usually at vertex) and the silver disc to which the respective grid lead is attached. And while the terms "frontal" lead and "occipital" lead are commonly employed in the following descriptions, it is understood that the deflections referred to are not due to potentials about the silver disc in question but represent the total potentials between the disc (in the frontal or occipital region as the case may be) and the grounded centre of the amplifying systems either at the vertex or over the point of interest. The terms "different" and "indifferent" as applied to such electrodes are false and misleading and the philosophy associated with the use of these terms has resulted in many unfortunate misconceptions.

Electro-encephalogram

The electrical phenomena which arise from the brain in both normal and pathological conditions and are detectable at the scalp may be roughly classed as periodic (rhythmic) and aperiodic (irregular). While it is possible that the

* Presented before the American Neurological Association, Atlantic City, May 3, 1938

brain might under some circumstances give off waves of almost any frequency between one cycle in five or more seconds and 35 cycles per sec. or higher, there seem to be certain frequency bands into which most of these waves fall, and certain frequencies which are not often seen. The common frequency bands in the encephalographic spectrum are roughly:

(a) below 1 per second	pathological or during sleep
(b) 1 to 3 per second	
(c) 6 per second	
(d) 7.5 to 11 per second	normal
(e) 14 per second	
(f) 18 to 35 per second	

Fig. 1 represents a rough estimate of the brain wave spectrum obtained from the electro-encephalograms of a considerable number of our patients.

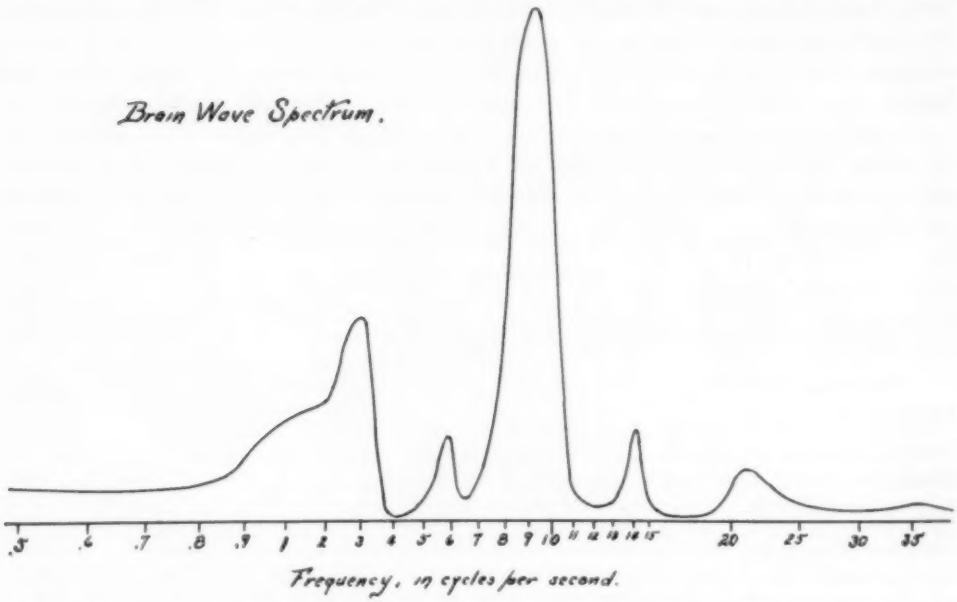


FIG. 1. Showing relative incidence of human brain wave frequencies in a group containing about 50 per cent of patients with some cerebral lesion.

While the ordinates of this curve represent the number of times of appearance of waves of any one frequency, it must be emphasized that the curve is estimated since no adequate quantitative compilations have yet been made. Others will doubtless place much less stress upon the three- and six-cycle bands, which have been here augmented by a considerable experience with patients subject to minor epileptic seizures. It should be noted that the valleys in the picture are perhaps just as significant as the peaks; a frequency of 4 per sec. is uncommon and the appearance of 7 per sec. rhythm is not relatively common. While many higher frequencies than those here represented are

encountered, their nature and significance are not sufficiently understood for discussion.

Roughly speaking, those frequencies which lie between 8 and 40 per sec. seem to be "normal" and healthy, although their absence or their relative amounts when present may be of considerable pathological significance. Those frequencies which lie below 8 per sec. appear to be pathological and to accompany abnormal conditions, with the possible exception of sleep in which slow waves are seen[1,2,3] but in which their frequency is seldom maintained long enough to count at any definite figure.

The aperiodic or irregular phenomena are more difficult to describe, and are composed largely of transients, which die out too quickly to be counted at any definite frequency, of transitional and rapidly changing forms and also of more or less definite figures such as "spikes" and "saw-tooth" forms which probably represent relatively isolated cortical discharges. These spikes, at least when present in considerable numbers, point strongly to an abnormal condition although cases with moderate numbers of isolated spikes are not uncommonly seen in which confirmatory evidence of pathology has not been found.

Swings of potential not sufficiently regular or sinusoidal to merit the term of waves are common in the very low frequency region where they may appear quite irregularly or fairly regularly at rates of from one in 10 seconds to perhaps one in 2 seconds. Such swings are seen in sleep and in many pathological conditions. They are also seen in anaesthetized subjects and in those with increased intracranial pressure[4]. Their presence in connection with tumors is not uncommon and while of probable value in suggesting such lesions they may not always have localizing significance.

Tumors and some other lesions usually give rise to slow waves and sometimes spikes, which undoubtedly arise from the disturbed tissue around the tumor[5]. These electrical phenomena may be quite sharply localized and by them the position of the tumor may often be rather well determined. Walter[6] has presented several cases in which such localization has been made by the presence of 3 per sec. waves which he has called delta waves. This particular frequency, although often seen about tumors, is, however, not necessarily indicative of tumor or other irritative lesions but seems to be a rather fundamental wave-pattern for children with minor epilepsy[7]. Most of the waves which are seen about tumors and which might well be all classed as delta waves range in frequency from about 0.5 per sec. to about 4.5 or 5 per sec., the most common frequency being 1 or 2 per sec. Such waves at frequencies greater than 3.5 per sec. are rare.

II. Localizing Phenomena

In the 11 cases presented here, 8 instances of cerebral tumor and 3 of cerebral scars, the findings in the electro-encephalogram which indicated the presence of a localized cerebral lesion were: (a) regular waves with a frequency of one to 3 per sec.; (b) very slow swings in potential varying from

one in five to one in two seconds; (c) irregular sharp or saw-tooth spikes; (d) electrical phenomena characteristic of localized convulsive seizures; and (e) absence of normal alpha waves.

(a) The most common localized electrical phenomena indicative of underlying pathology were waves occurring at the frequency of one-half to three cycles per second. Waves of around 3 per sec., as has been pointed out, are characteristic of children suffering from petit mal. In such instances, however, they are not localized. In the cases presented in this paper these waves arose from a localized area referable to the lesion. They were present in seven of the eleven cases (Nos. 1, 2, 4, 7, 8, 10 and 11). In 3 of these cases (Nos. 4, 8 and 11) their frequency was about one per sec.; in 3 (Nos. 2, 7 and 10) it was 2 per sec.; and in one (No. 1) it was 3 per sec. It is obvious that the slower frequencies, one or two per sec., are the most common. In all instances these waves were most marked and most constant at or very near the site of the lesion. In 2 cases (Nos. 8 and 10) they were confined to that region. In 2 cases (Nos. 7 and 11) and possibly a third (No. 4) they were less constant and of smaller amplitude in other portions of the same hemisphere. As these waves obtained at a distance from the lesions were nearly in phase with the more prominent waves, it seemed likely that they were propagated from the region of the lesion. In some cases records obtained from two points on opposite sides of the region of greatest intensity would give waves which were 180° out of phase with each other (see Case No. 1). In two instances (Nos. 1 and 2) synchronous waves, less constant and of lower amplitude, could be obtained from the same lobe of the other hemisphere.

(b) In 4 cases (Nos. 1, 3, 9 and 11) very slow but regular swings in potential ranging from once in five seconds to once in two seconds could be obtained. In Case 1, in which there was a well circumscribed astrocytoma of the left frontal lobe, such waves were obtained from both frontal lobes. The same was true of Case 11, but here necropsy revealed that the tumor had spread through the corpus callosum to involve the other frontal lobe. In Cases 3 and 9, instances of a superficial cortical scar and traumatic subarachnoid cyst, and of a cystic glioma of the left occipital lobe respectively, this phenomenon was limited to the site of the lesion.

(c) Sharp, sudden alterations in potential giving rise to spikes may occur singly, irregularly, or regularly in brief runs. Such spikes as previously noted, are apparently significant only when present in considerable numbers. The runs are particularly worthy of note. Such spikes were prevalent in 4 cases (Nos. 1, 5, 6 and 7). In Case 5, a meningioma of the superior right precentral region, and in Case 6, a traumatic scar in the right frontal region, the spikes were localized to the area of the lesion. In Case 7, a meningioma of the posteroinferior part of the left frontal lobe, a few asynchronous spikes were obtained from the opposite frontal lobe and some spikes of lower amplitude but synchronous with those from the left frontal region were obtained from other parts of the same hemisphere. In Case 1, a circumscribed left frontal astrocytoma, a few asynchronous spikes were obtained from the opposite right frontal region.

(d) In one case (No. 3) in which there was extensive scarring of the dura mater, arachnoid and pia mater over the right frontal lobe associated clinically with generalized convulsive seizures, electrical phenomena characteristic of those obtained from individuals suffering from localized convulsive seizures were obtained only from the right frontal region. These did not spread to any other region and were not associated with any objective or subjective evi-

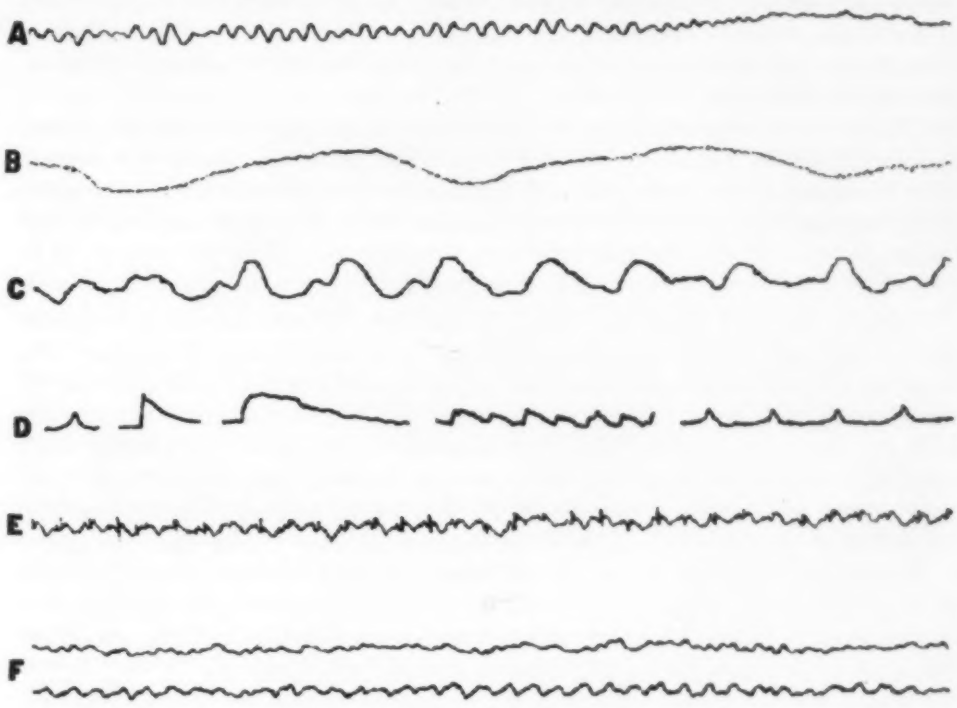


FIG. 2. Showing (except line A) the electro-encephalographic configurations indicative of localized cerebral pathology. Line A is a normal tracing starting with the eyes closed, showing a fairly prominent alpha wave which disappears at the end of the line where the eyes are opened. Line B shows slow waves having a frequency of 0.5 per sec. Line C shows 2 per sec. delta waves. Line D shows cusp-shaped and saw-tooth spikes, singly and in runs. Line E shows the electrical manifestation of a localized epileptic seizure. Lines F show the absence of alpha waves (upper tracing) from the occipital lead on the side of a tumor and simultaneously the presence of alpha waves (lower tracing) in the occipital lead from the unaffected side. All these tracings are to the same scale in voltage and in time.

dence of a seizure. This characteristic electrical phenomenon is the typical "wave and spike pattern"[8] which has come to be looked upon as pathognomonic of minor epilepsy. In this case the total deflection of the localized seizure was around 40 microvolts and the duration of the seizure one to two minutes (in contrast to the usual petit mal deflection of around 200 microvolts with a seizure duration of about 10 to 15 seconds).

(e) In 2 cases (Nos. 2 and 9) an absence of the normal (8 to 10 per sec.) alpha rhythm was obtained. In Case 2 this absence was found only on the

side of the lesion—a large localized traumatic cerebral atrophy extending from the cortex to the ventricle in the left parietal region, the surface of which had been surgically removed. In Case 9, a cystic glioma of the left occipital lobe, the alpha rhythm was absent from both occipital lobes, whereas localizing slow shifts of potential were present (left side). However, these electro-encephalograms were obtained following attempted ventriculography during which the cyst on the left side was evacuated, while on the right side, because of an anatomical abnormality, the needle was inserted down the calcarine fissure resulting in a temporary left homonymous hemianopsia and a permanent small paracentral scotoma.

The features which have been noted above as indicative of cerebral lesions are illustrated in Fig. 2, which is a composite made up of episodes clipped from various records. This figure shows the principal electro-encephalographic configurations which we believe are indicative directly or indirectly of cortical lesions.

III. Discussion

In all of these 11 cases the pathology has been determined either at operation or autopsy, or has been demonstrated by pneumoencephalography. The location of the pathology and the approximate localization indicated by electro-encephalography have been in substantial agreement. In one patient with a large brain tumor (Case 11) only small waves indicating a lesion were obtained. This patient had had a subtemporal decompression which may have reduced the pressure on the cortex. A total of 13 patients having cerebral lesions later confirmed by operation, autopsy or both, have been examined by electro-encephalography in the last twelve months, from which the above 11 cases have been chosen. All of these have shown some evidence suggestive of an intracranial lesion. No attempt has yet been made to evaluate the electrical possibilities in posterior fossa lesions or in pituitary disorders.

Waves having frequencies from 0.5 to 3 per sec. which are sensibly equidistant from peak to peak for at least five cycles seem to be quite characteristic of tumors but are also seen with other types of localized pathology. With the exception of waves at about 3 per sec. commonly seen with minor epilepsy, but not so distinctly localized or lateralized as with tumors, such waves have always, when obtained from patients while awake, indicated gross cerebral pathology. It should be noted that waves of this frequency can be simulated by rhythmic eye movements or rhythmic movements of the eyelids but these artifacts appear only in the frontal leads and are equal and simultaneous on the two slides.

The very slow swings—less than 0.5 per sec.—are found in many pathological conditions, particularly the chronic degenerative diseases and chronic encephalitis. While such slow shifts of potential are seen in connection with cerebral tumors they are not peculiar to them. In most conditions they appeared most commonly and prominently from the frontal lobes. Only when they are localized to one area of the head, as in Cases 3 and 9, can they be considered to have any localizing value.

The records obtained during sleep may at times be confusing. In sleep many slow transitional forms are seen. Occasionally quite regular runs are present, often around one per sec. It should be noted whether the patient is sleeping and whether such waves are localized to any single area. Great care must be exercised in the interpretation of the various signs. This is particularly true in the matter of spikes; an occasional isolated spike carries little weight, but when seen in considerable numbers or in series they seem to imply an abnormal cortical discharge.

The absence of alpha waves from the occipital leads or their gross inequality in corresponding areas on the two sides should arouse suspicion and is at times corroborating evidence but at the present time does not in itself carry much weight. The appearance of the electrical manifestations typical of localized epileptic seizures is rare. They probably have great localizing and diagnostic importance. Theoretically, few waves should be obtained over areas where the cortex is atrophic or where there is a cyst. We recall a case in which considerable activity was present in frontal, temporal and occipital leads and appeared of almost the same form in these three leads simultaneously. Operation revealed a large porencephalic cyst in the posterior frontal region, over which the cortex was so thin and gelatinous that it probably had little, if any, function. It seems probable that most of the electrical activity was here transmitted up from the neighboring intact regions.

It is perhaps unnecessary to emphasize that abnormal waves, especially those from 0.5 to 3 per sec., come in trains or spindles, and that their amplitude varies from time to time. Because of this, multiple simultaneous recording from several areas of the head is essential for any certainty of localization. It is felt that while the method of electro-encephalography is of necessity somewhat indefinite in the outlining of cerebral tumors and other lesions, it does, nevertheless, compare favorably in this regard with many of the methods now in use, and that there are many lesions which it is possible to indicate more or less definitely by this means where other methods give only negative findings. In view of these possibilities it seems likely that electro-encephalography will become an essential adjunct in the localization of intracranial lesions.

IV. Summary

Electro-encephalography presents an easily applied, non-tiring and non-traumatizing, relatively simple means of localizing many cerebral lesions, particularly with reference to tumors and other focal lesions. Intracranial lesions are indicated and may usually be localized by the following electro-encephalographic phenomena:

1. Very slow swings, 1 to 2 in 5 seconds.
2. Slow waves from ½ to 3 per sec.
3. Spikes and saw-tooth forms.
4. Electrical manifestations of localized epileptic seizures.
5. Absence of or marked difference in the alpha rhythm on the two sides.
6. Marked diminution or localized absence of electrical activity.

Eleven cases are presented in all of which the lesions have been localized more or less accurately by this method and which collectively show most of the above features. In 8 of these cases tumors were present, in 2 there were cerebral scars which had resulted from trauma, and in one there was a marked scarring of the meninges. All have been confirmed by roentgenograms, operation or necropsy.

It is suggested that the electro-encephalographic method will become a valuable adjunct in the diagnosis and localization of intracranial lesions.

Case Reports

Case 1. (C. R. M., No. 177797), a white male, 36 years of age, was by referred Dr. Harold Evans of Davenport, Iowa. He was well until seven years prior to admisson on

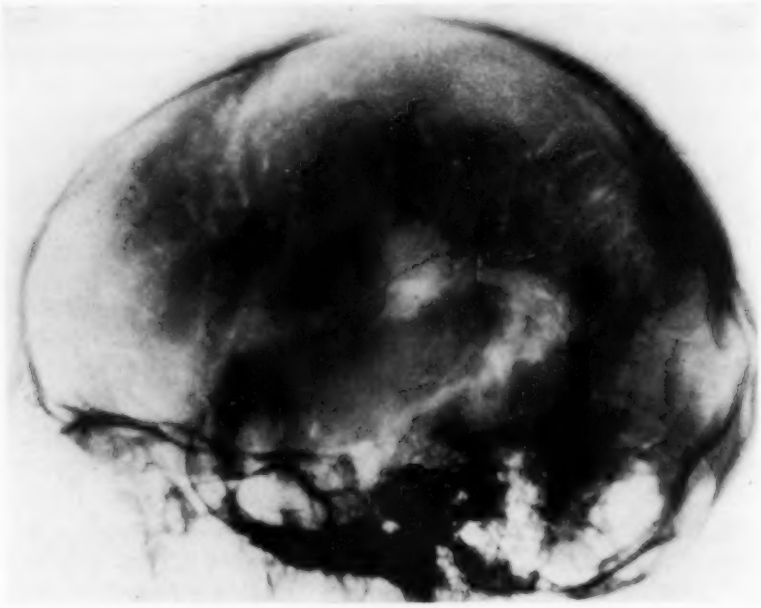


Fig. 3. Case 1. This pneumo-encephalogram shows the anterior portion of the left lateral ventricle displaced downward with a large filling defect in the posterior part of the displaced area which was caused by a nodule of tumor within the lateral ventricle.

June 23, 1937. The onset of his present illness was with a right-sided convulsive seizure. Subsequently he had many such attacks and some generalized seizures in all of which however, he lost consciousness. Following many of these attacks he experienced a temporary difficulty in speaking and weakness of his right extremities. During the last year he had developed increasing difficulty in speaking and slight weakness in the right upper extremity.

Examination revealed only a definite motor aphasic defect and some awkwardness in rapid movement of the right hand. Pneumo-encephalography indicated a large tumor in the left posterior frontal region (Fig. 3).

The electro-encephalogram showed very slow negative swings in the frontal leads only. These were irregular but often came at a rate of about one in 5 seconds. Three per second waves, large and regular, were seen in the lead from the mid-line of the frontal region, propagated slightly into the right frontal region, and were absent in the occipital areas

(Fig. 4). Here, as in all subsequent figures, the circle represents the common point of the amplifying systems, the dots represent the points at which the individual amplifiers are applied. When the center point of the amplifying system was shifted over the left frontal lobe and the amplifiers spread out fanwise as in the sketch, Fig. 4B, these waves were seen in all three leads, largest in the anterior lead, smaller toward the vertex, with a gradual phase shift around the central point so that the voltage in the lead towards the temporal region is 180° out of phase with the voltage in the lead towards the midline frontal region. This is well shown in Fig. 4 and suggests that the source of these waves lies somewhat anterior to the center point of the amplifying systems. Sawtooth spikes were seen in the lead from the left frontal region. These were irregular but quite numerous in this area and

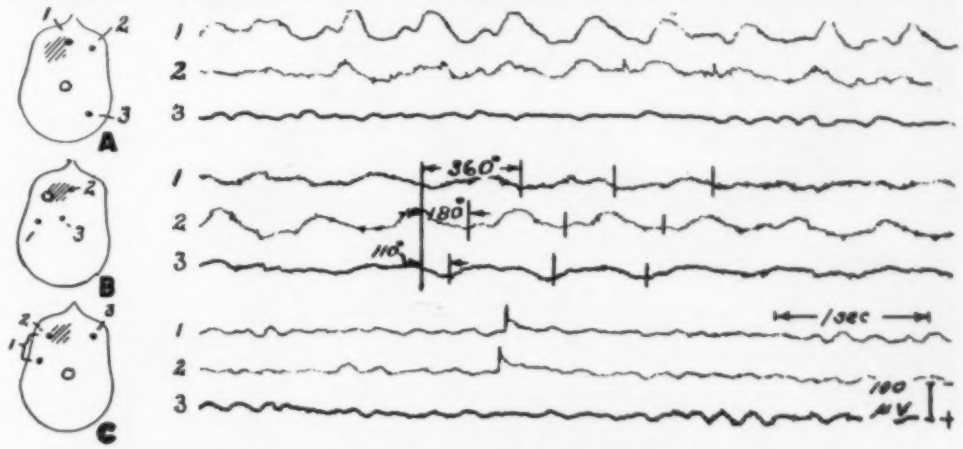


FIG. 4. Case 1. Delta waves at A_1 arising from the mesial aspect of a tumor.

seemed to come in showers. Occasional similar spikes, much smaller and much less numerous, were seen from the right frontal area. Some spikes from the left frontal area are shown in Fig. 4C. (In Fig. 4C, lead 1 records the voltage between the left temporal and left frontal regions, leads 2 and 3 between the left and right frontal regions respectively and the vertex.) From this electro-encephalogram it was concluded that there was a lesion lying in the mid-portion of the left frontal lobe.

Subsequently, on June 29, 1937, the patient was operated upon and a large, well circumscribed benign glioma (astrocytoma) which measured 7 cm. in diameter on the surface was removed from the substance of the left frontal lobe. The tumor lay 1 cm. medial to the superior longitudinal fissure, 1 cm. anterior to the precentral vein and 2 cm. above the Sylvian vessels. The tumor was cone shaped, the base presenting on the surface of the brain, the apex extending inward to the lateral ventricle, with a small nodule of tumor actually lying within the anterior horn of the ventricle. The patient made an uneventful recovery.

CASE 2. (H. J. P., No. 143696), a boy 19 years of age was referred by Dr. Albert H. Montgomery of Chicago. This boy was well until the age of 5 when he sustained a compound depressed fracture of the skull in the left posterior parietal region. This was treated surgically and the boy was quite well, except for some slight weakness of the right extremities, until the age of 13 when he began to suffer from convulsive seizures involving the right arm only. These attacks were preceded by an indescribable visual aura. On only two occasions did the patient lose consciousness. The attacks occurred about 3 times a week in spite of the administration of phenobarbital and bromides.

Examination showed a large soft pulsating defect in the bone of the left parietal area. There was some spasticity of the right arm and leg and some difficulty in making rapid movements. Sensory perception was slightly reduced on the right side and stereognosis in the right hand grossly impaired. Babinski's sign was present on the right. Pneumoencephalogram revealed a large dilatation of the left lateral ventricle at the genu with considerable regional atrophy of the brain.

At operation on January 24, 1936 the cortex in the affected area was found to be avascu-

lar and gelatinous and was very thin, with a much dilated genu of the ventricle immediately beneath. All of the cortex overlying the ventricular dilatation was removed. Since then there has been no recurrence of the convulsions.

After 4 months he was readmitted for further study. Electro-encephalography done at that time revealed an absence of alpha waves on the left side and their definite presence on the normal side. (This finding is directly opposed to that of Lemere[9] who found alpha waves absent on the unaffected side and present on the side of a lesion.) Good runs of waves at about 2 per sec. were seen especially in the left frontal lead but also to a lesser extent in the right frontal, pointing to a source of irritation somewhat to the left and forward of the vertex. This is seen in Fig. 5A. In Fig. 5B are seen 3 simultaneous tracings showing 2 per sec. waves in the left frontal, 8 per sec. waves in the right occipital and nothing definitely periodic in the left occipital lead. The cause of the 2 per sec. waves is here most probably some cicatricial contraction at the anterior end of the cortical defect which has been indicated by shading in the sketch in Fig. 5.

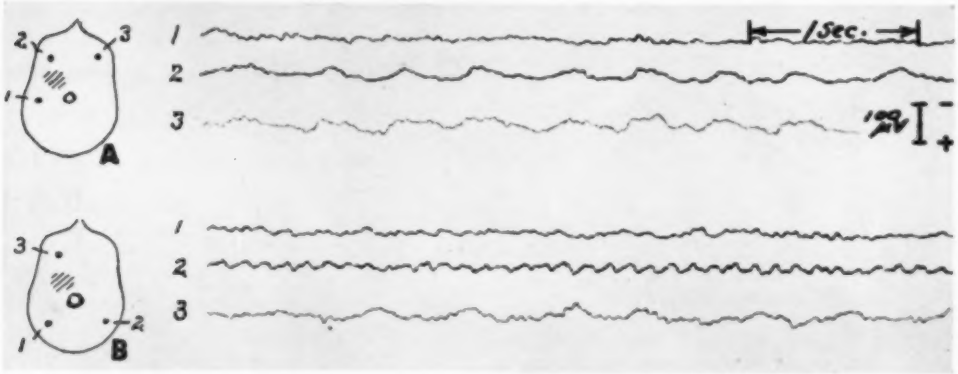


FIG. 5. Case 2. Delta wave at A_2 and B_3 arising from the anterior aspect of a scar, and at B_1 absence of alpha waves on the side of the lesion.

CASE 3. (L. B., No. 137071), male, 25 years of age, was referred by Dr. L. E. Dupes of Hobart, Indiana. He was perfectly well until the age of twenty-one years when he suffered from a nocturnal generalized convulsion. During the following four years he had about six such seizures. Recently severe headaches had developed. Just prior to his admission January 28, 1937, he suffered from a series of attacks in which he lost consciousness but had no convulsion. Examination revealed a bony prominence over the right frontal sinus. There was an anosmia on the right side, a slight left lower facial weakness, and the left platysma myoides did not contract. There was a questionable sign of Babinski on the left side. Roentgenograms of the skull revealed a large osteoma in the right frontal sinus with several knob-like protrusions of the osteoma through the inner table of the skull.

Electro-encephalography revealed slow waves having a frequency of one every two seconds localized to the right frontal lobe, and localized epileptic seizures in this area which did not spread to other areas and did not produce any clinical evidence of a seizure. Indeed, he would talk and answer questions during a seizure and denied any knowledge that anything unusual was occurring. These seizures occurred also while he was asleep and during sleep also there was no clinical evidence of an attack. The voltage associated with these attacks was of the order of about 40 microvolts total deflection, and the attacks lasted about one minute, that is, considerably longer than most minor attacks.

These slow waves are shown in Fig. 6A where they are seen with tracings taken simultaneously from other areas. At B is seen the typical manifestation of a localized epileptic seizure. It was obtained only from the right frontal region. The tracing showing this seizure has been enlarged two diameters at C to show more clearly the typical "hump and spike" formation.

The patient was operated upon on February 2, 1937. A right frontal osteoplastic flap was reflected and a large osteoma was removed from the frontal sinus. It possessed five knob-like protrusions which penetrated the inner table of the skull and the dura mater

and were embedded in the brain. The dura mater had of necessity been opened in removing these bony knobs. It was firmly adherent to the underlying arachnoid membrane throughout all of the exposed area, *i.e.*, over the right pre-frontal area. There was extensive fibroblastic proliferation involving all of the meninges in this region. How far beyond the operative field this process extended could not be stated. It appeared likely that it was the result of a low grade infection that had penetrated the subdural space from the frontal sinus along these bony protrusions. There has been no recurrence of the convulsive seizures since the operation. Phenobarbital has been taken regularly.

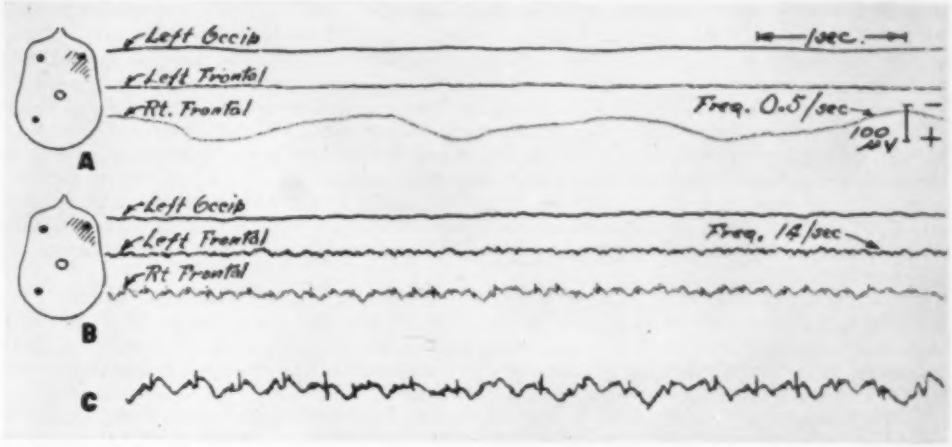


FIG. 6. Case 3. Right frontal lead over meningeal scarring shows at *A*, ½ per sec. delta waves and at *B*, subclinical epileptic seizure pattern, localized to this area. At *C*, seizure pattern enlarged two diameters.

CASE 4. (J. O., No. 155035), a male, 51 years of age, was admitted to the University of Chicago Clinics on July 6, 1936 complaining of attacks which had been present for three months. These attacks began with a bad taste in his mouth, occasionally the smelling of an unpleasant odor, he would then become nauseated and his hands would shake. He did not lose consciousness. On examination the only findings were a marked euphoria and a persistent attempt to joke and make witty remarks. The visual fields were normal. A ventriculogram was made which indicated a tumor deep in the substance of the right temporal lobe.

He was operated upon on July 11, 1936. An extensive infiltrating glioma was found deep in the right temporal lobe extending into the basal ganglia. The overlying cerebral cortex of almost all of the temporal lobe was removed and a large part of the glioma.

Electro-encephalography was done about two months after the operation and as we were at that time looking only for changes in the alpha rhythm due to tumors, only occipital leads were taken. They show a wave having a frequency of slightly greater than

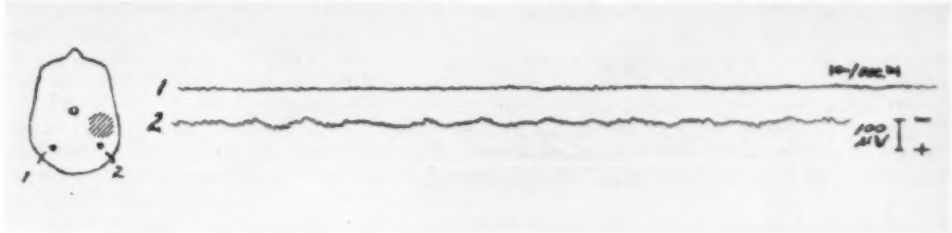


FIG. 7. Case 4. Delta waves from posterior aspect of lesion; none from opposite (not involved) side.

1 per sec. in the right occipital area, in contrast to the left occipital region which shows nothing of this nature. Whether this wave, which may have been larger further forward, was caused by the remaining tumor or was due to some pathology resulting from the operation, is impossible to say. Small alpha waves are seen in both occipital leads, in the right superimposed on the one per second waves. These findings are seen in Fig. 7 which shows a section of the record taken in this case.

CASE 5. (P. H., No. 169364), a white female, 47 years of age, was referred by Dr. A. G. Miller of Hobart, Indiana. Since the age of 39 she had suffered from weakness and numbness of the left lower extremity which had begun in the toes and grown progressively more severe and extensive. For the past 7 years she had suffered from convulsive seizures limited to the left upper extremity until the last year when the attacks had become generalized and were accompanied by loss of consciousness. Examination revealed considerable weakness and spasticity of the left lower extremity. She was unable to move the toes or ankle voluntarily and walked with a hemiplegic limp. There was no disturbance in the cranial nerves. Sensation was intact. In the left upper extremity there was moderate weakness of movement at the shoulder and elbow and some slight spasticity. Rapid alternating movements were impossible in this extremity. There was slight atrophy of the musculature about the shoulder. Tendon reflexes were all increased on the left side, the abdominal reflexes were absent and Babinski's sign was present. Roentgenograms of the skull revealed no abnormality.

Electro-encephalography showed a large number of irregular discharges usually of a saw-tooth form, sometimes singly but sometimes so fast and regular as to give almost a sinusoidal appearance. These appeared in the right posterior frontal area and were localized to this region. There were no slow waves or delta waves. Fig. 8 shows two runs of these saw-tooth discharges both appearing in the right frontal lead.

At operation on March 18, 1937 a small parasagittal meningioma was found over the right central gyrus just lateral to the superior longitudinal sinus. It lay astride the central vein which was greatly engorged. The tumor was removed.

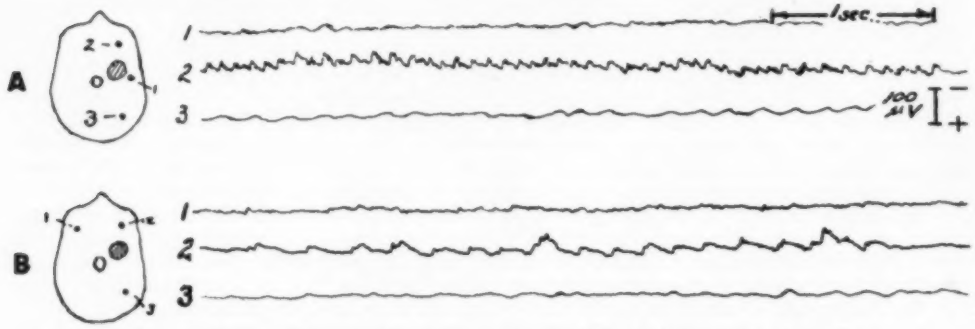


FIG. 8. Case 5. Saw tooth pattern, A_2, and B_2, in long runs, sharply localized to anterior aspect of small meningioma.

CASE 6. (J. S., No. 176916), male, 22 years of age, was admitted to the University of Chicago Clinics on July 2, 1937 complaining of "fainting spells" which began two years before. At the age of 2 years he had fallen from a third story window and sustained a severe deforming fracture of the skull as a result of which an irregular bony prominence had persisted in the frontal region. He was unconscious for a time following this accident and lost the power of speech for the succeeding 6 months. Since this accident movements of the right arm and leg had been weak and awkward and he was lethargic and mentally retarded, reaching only the fifth grade in school. At the age of 18 he was involved in an automobile accident in which he was thrown from the car into a snowbank but suffered no ill effects. When 20 years of age he suddenly lost consciousness without warning and for no apparent reason, and then developed a generalized convulsion which was so severe as to throw him out of bed. Since then these attacks have recurred about once every month. Examination revealed a bony ridge about 6 inches long running along the coronal suture and another

spherical elevation a short distance posterior to this ridge on the left. He was apathetic and responded slowly to all questions. At times he stammered and had difficulty in finding words. It was difficult to hold his attention and sensory examination was unsatisfactory. The right upper extremity was somewhat smaller than the left and, although there was no weakness, he was markedly awkward in all movements of this extremity and it did not swing as he walked. The tendon reflexes were all slightly hyperactive on the right side, the abdominal reflexes were absent on that side but Babinski's sign was not elicited. Roentgenograms of the skull revealed an extensive bony deformity along the coronal suture on

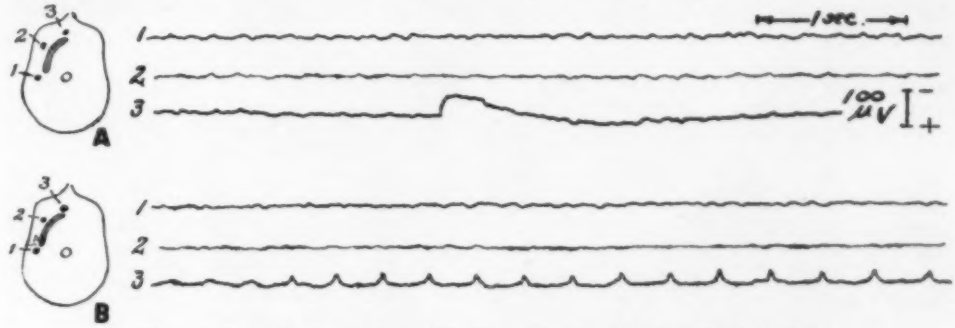


FIG. 9. Case 6. Cusp shaped spikes, B_3, sharply localized to the anterior end of a long cortical scar.

the left side and extending backward into the left parietal bone. Pneumo-encephalography revealed some enlargement of the left lateral ventricle and a large defect in the cerebrum beneath the bony deformity.

Electro-encephalography showed irregular spikes, mostly cusp-shaped, singly and in runs, rather sharply localized near the anterior end of the deformity of the left frontal bone. None was obtained from other areas. Fig. 9 shows a run of cusp-shaped spikes and a single more saw-toothed form obtained from this area.

CASE 7. (F. K., No. 185650), a white female, 49 years of age, was admitted to the University of Chicago Clinics on November 7, 1937 complaining of convulsions. These had begun in October, 1936 and she had suffered from seven such seizures. In these attacks she would suddenly and without warning lose consciousness, the face and jaw would be drawn to the right, all extremities becoming rigid, and she would froth at the mouth. Following

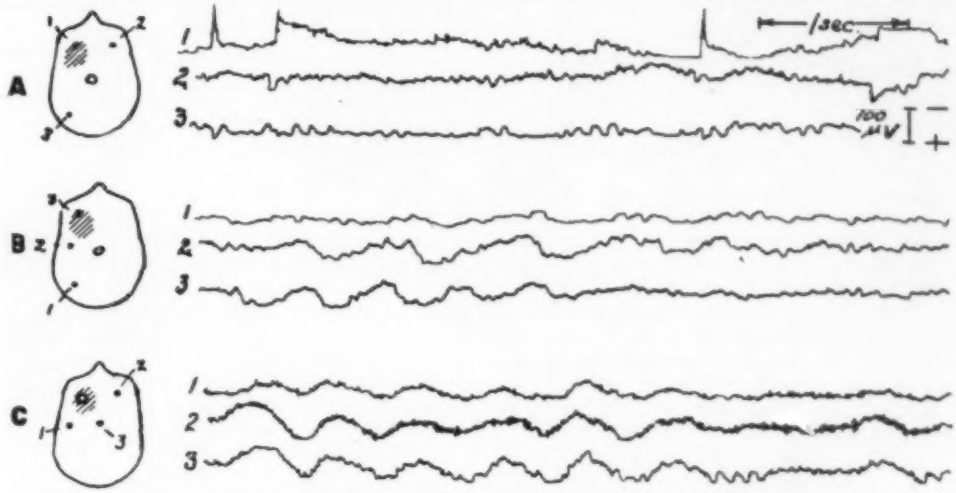


FIG. 10. Case 7. Delta waves from the neighborhood of a tumor at B_2 and B_3.

each attack she would be unable to speak for from several hours to two days. Ever since the first convulsion there had been some persistent difficulty with speech. In addition to these major attacks there had been many minor seizures of short duration in which she did not lose consciousness but was wholly unable to speak, although she insisted that she knew what she wished to say. Since March, 1937, she had been unable to read and, although able to write, could not spell correctly. Examination revealed inability to form a coherent sentence including three simple words which were given to her, or to relate the contents of a single sentence read from the newspaper. Enunciation was very poor. There was a slight right lower facial weakness and a very slight weakness of the right upper extremity. Rapid

FIG. 11. Case 8. Large calcified oligodendroglioma in the medial portion of the left frontal lobe. In this ventriculogram the slightly dilated right ventricle which is normal in shape can be faintly seen. There is only a small amount of air in the left lateral ventricle, the anterior horn of which has been cut off and displaced backward. This ventricle communicates with a series of cysts in the superior part of the frontal lobe.

alternating movements were done less well by the right hand. All tendon reflexes were hyperactive on the right side. Babinski's sign was not present. The findings on lumbar puncture were normal. A pneumo-encephalogram revealed that the anterior horn of the left lateral ventricle was shifted slightly toward the right.

Electro-encephalography showed sharp spikes, most prominent and most frequent in the left frontal area. They were also seen in the left temporo-occipital and right frontal areas where they were rounded but synchronous with those in the left frontal area and probably transmitted from it. The right frontal area also showed a few sharp spikes which were not associated (synchronous) with anything seen elsewhere. Spindles or brief runs of regular waves of about 2 per sec. were seen in the left frontal and temporal leads, usually somewhat larger in the frontal. These waves were transmitted to other areas but were very small there, as is seen in the left occipital lead of Fig. 10. This figure shows at (A) spikes from the left frontal area, and (B) 2 per sec. waves from the left frontal and temporal areas, the temporal appearing to be somewhat slower, and at (C) the reference point has been shifted to the left frontal area, giving waves in all three leads. The fact that they are all in

phase and of nearly the same amplitude indicates that the reference point was in the vicinity of the disturbance.

At operation a meningioma about the size of a tennis ball was found lying in the inferior part of the posterior frontal region, its inferior margin about 3 cm. above and anterior to the central sulcus. Since operation phenobarbital has been administered and she has had no further convulsions and her speech has steadily improved.

CASE 8. (C. C., No. 185438), a white male, 53 years of age, was admitted on October 17, 1937 complaining of "fainting spells." In April, 1937, he had had his first generalized convulsion which occurred without warning and without any focal phenomenon. In May, 1937, 4 more such seizures occurred in one day. There were no more until September of that year when he began having them at frequent intervals. His wife had occasionally noted attacks of jerking of the right leg while the patient was in bed at night. On examination he was apathetic, disinterested in his surroundings, and paid no attention to his mail or the newspaper. He was quite unconcerned about his condition or the proposed operation

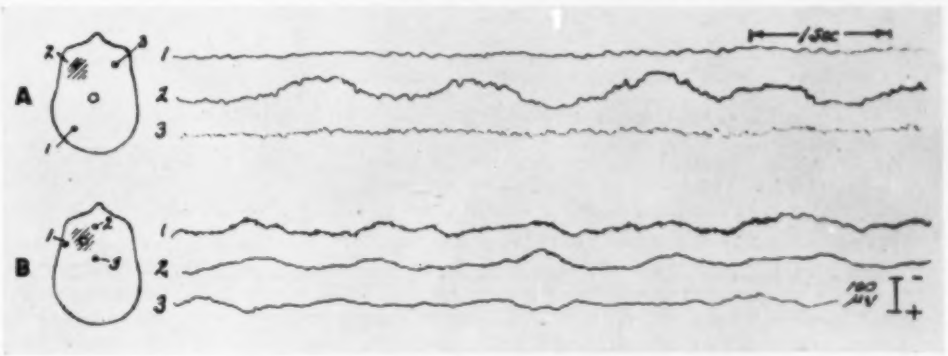


FIG. 12. Case 8. Delta waves over tumor, at A_2.

and rarely spoke except in response to direct questions. There was, however, no demonstrable aphasia. There was a questionable weakness of the facial musculature on the right and of the right upper extremity. The tendon reflexes were somewhat more active on the right side. Babinski's sign was not present. Roentgenograms of the skull revealed a large area of calcification in the left posterior frontal region. Ventriculography indicated a tumor in the area of calcification containing a cystic cavity which communicated with the lateral ventricle. Fig. 11 shows this calcification and the distortion of the ventricle backward and downward by the tumor.

Electro-encephalography showed spectacular runs of waves of a frequency slightly less than one per second, almost continuous and sharply confined to the left frontal lobe. These are seen in Fig. 12, and at (B) the central point of the amplifying system has been placed on the left frontal area, the points to the individual amplifiers being grouped about it at a radius of about two inches. Waves are seen in all leads suggesting that their point of origin probably lies within the circle formed by these leads. From the phase relation and relative size of these waves, the direction of propagation was deduced to be from in front backwards (across the area from which voltages are picked up) and the source somewhat in front of the center point of the amplifying systems

At operation on October 26, 1937 the surface of the cortex of the left frontal lobe showed definite signs of pressure, the convolutions being flattened but not much discolored. A large glioma was found deeply situated and apparently passing into the corpus callosum. The anterior two-thirds of the frontal lobe was amputated and a large part of the tumor removed. It proved to be an oligodendroglioma.

CASE 9. (M. D., No. 459), a white female, 26 years of age, was referred by Dr. M. M. Hoeltgen of Chicago. She was admitted on September 27, 1937. For 10 years prior to admission she had repeatedly experienced brief attacks of flickering lights before her eyes. These were not lateralized. They were not associated with any other phenomenon until one year before admission when the seizures became more frequent and were associated with severe headaches, nausea and at times vomiting. Examination revealed a bilateral

papilloedema of 2 to 3 diopters. The right pupil was slightly larger than the left but both reacted normally. The visual fields were full on repeated examination. There were no other abnormal findings. A ventriculogram was attempted. The needle inserted into the left occipital lobe encountered a cystic cavity at a depth of 2 cm. from which syrupy yellow fluid was obtained.

Electro-encephalography showed absence of alpha waves on both sides even when the amplification was increased to several times that normally employed. Slow negative swings were seen chiefly in the left occipital lead. These were irregular but at times came about twice in 5 secs. Such a succession of swings is seen in Fig. 13 where they appear from the left occipital lead in contrast to the right occipital which shows nothing. It is probable that they represent localized pressure in this area. No definite waves in the neighborhood of 1 or 2 per sec. were seen.

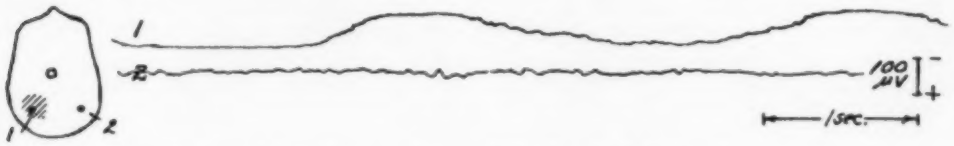


FIG. 13. Case 9. Slow swings localized to area of tumor.

At operation a large glioma (atypical astrocytoma) was found occupying most of the left occipital lobe. The entire lobe including the tumor and the cystic cavity was amputated. She made an excellent recovery except for a persistent right homonymous hemianopia.

CASE 10. (G. Z., No. 125436), a white male, 34 years of age was referred by Dr. A. H. Barnett of Chicago. He was admitted on December 3, 1937. Three years previously he had suffered his first attack. It began with a "numb" feeling in the epigastrium, an inability to speak, then loss of consciousness and a generalized convulsion. At first these attacks occurred at intervals of three to four months but just prior to admission had grown more frequent. From the first there was an associated slight weakness of the right arm and frequent twitchings of the right leg when in bed at night. During 1937 he had several attacks in which he would not lose consciousness but the right arm and leg would "draw up" and he would lose the power of speech. Examination revealed no abnormality except that rapid alternating movements were performed poorly by the right upper extremity.

Electro-encephalography showed delta waves, usually rather irregular, but sometimes sharp and clear at a frequency of about 2 per sec. These were quite sharply confined to the left frontal area. Fig. 14 shows tracings from the left frontal, right frontal and right temporal areas. Two per sec; waves are seen in the tracing from the left frontal area only.

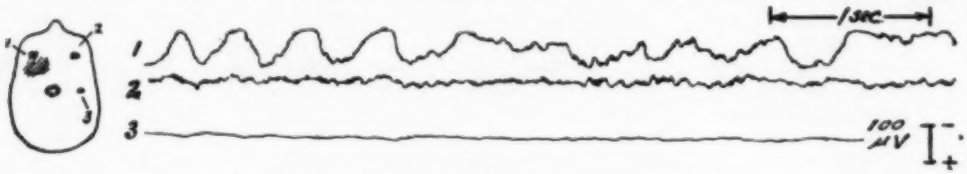


FIG. 14. Case 10. At 1, delta waves over tumor.

Ventriculography showed displacement of the anterior ventricular system downward and to the right. At operation a large glioma (astrocytoma) was found occupying the central portion of the left frontal lobe, extending backward almost to the precentral sulcus. The antero-superior one-third of the left frontal lobe was amputated and the tumor extensively removed. He has had no further attacks and has made an excellent recovery.

CASE 11. (M. L., No. 115439), a white female, 34 years of age, was first admitted on May 19, 1935 complaining of left-sided convulsive seizures and weakness of the left side of the body. For 7 years she had suffered from three or four convulsive attacks a year. The convulsive movements involved only the left side of the mouth, the left arm and leg. In some of the attacks consciousness was lost. In September, 1933, she began to develop weakness of the left arm and in July, 1934, the left leg became similarly affected. This weakness grew progressively more severe. In July, 1933, a pneumo-encephalogram was performed

elsewhere which was said not to indicate the presence of a tumor. Examination revealed little or no facial weakness but a marked weakness with severe spasticity in the left upper and lower extremities. The tendon reflexes were all hyperactive on the left side and Babinski's sign was present. The abdominal reflexes were absent on the left side. Reflex forced grasping was present in the left hand. Sense of position was impaired in the fingers and toes on the left side.

At operation on May 25, 1935, a large glioma (astrocytoma) presented on the surface of the postero-superior portion of the left frontal lobe. It measured 6 × 5 cm. on the surface. It extended posteriorly to the anterior margin of the pre-central gyrus and inferiorly to the inferior margin of the second frontal convolution. An extensive block dissection was made.

Following this operation she continued to have a severe left hemiplegia. Convulsions were readily controlled with phenobarbital but returned whenever the medication was omitted. In June, 1937, she began to suffer from occasional attacks of severe headache, nausea and vomiting. On November 10, 1937, the decompression began to bulge markedly and she was readmitted on November 12, 1937. Examination revealed nothing additional.

At that time electro-encephalography was done. It revealed slow negative swings in both frontal leads equally. These occurred roughly about once in five seconds, were not seen in the other leads. Large alpha waves were present in both occipital leads and were also obtained, although in a more broken fashion and not so continuously, from the whole cranial surface. They appeared to be somewhat increased in amplitude. Over the region of the tumor occasional small runs of delta waves having a frequency of 1.3 per sec. were seen. They were of small amplitude and somewhat obscured by the concomitant faster disturbances which were largely of alpha frequency. Fig. 15 shows an electro-encephalographic tracing using two channels, one from each temporal region. The one on the right temporal region shows small 1.3 per sec. waves in contrast to the one from the opposite side which shows none. Marks have been placed below the record to emphasize the delta waves.

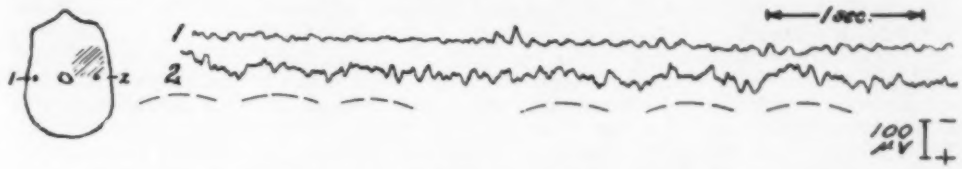


FIG. 15. Case 11. At 2, small delta waves from region of large tumor.

This patient died suddenly on the following day. Autopsy revealed on the right side a very extensive, deeply seated infiltrating glioma extending from the central sulcus about two-thirds of the distance to the tip of the frontal lobe, crossing in the corpus callosum and involving the left frontal lobe to some extent. This case is presented as an example of a large tumor with minimal findings. It is possible that the subtemporal decompression may have lowered the local pressure and reduced the electrical disturbances.

REFERENCES

1. LOOMIS, A. L., HARVEY, E. N., and HOBART, G. A. Cerebral states during sleep, as studied by human brain potentials. *J. exp. Psychol.*, 1937, *21:* 127–144.
2. GIBBS, F. A., DAVIS, H., and LENNOX, W. G. The electro-encephalogram in epilepsy and in conditions of impaired consciousness. *Arch. Neurol. Psychiat., Chicago*, 1935, *34:* 1133–1148.
3. BLAKE, H., and GERARD, R. W. Brain potentials during sleep. *Amer. J. Physiol.*, 1937, *119:* 692–703.
4. WALTER, W. G. The location of cerebral tumors by electro-encephalography. *Lancet*, 1936, *2:* 305–312.
5. FOERSTER, O., and ALTENBURGER, H. Elektrobiologische Vorgänge an der menschlichen Hirnrinde. *Dtsch. Z. Nervenkr.*, 1935, *135:* 277–288.
6. WALTER, W. G., and WYLLIE, W. G. The electro-encephalogram in the diagnosis of cerebral pathology. *Proc. Roy. Soc. Med.*, 1937, *30:* 578–579.
7. CASE, T. J. Electro-encephalography in the diagnosis and localization of intracranial lesions. *J. nerv. ment. Dis.*, 1938, *87:* 598–602.
8. GIBBS, F. A., LENNOX, W. G., and GIBBS, E. L. The electro-encephalogram in diagnosis and in localization of epileptic seizures. *Arch. Neurol. Psychiat., Chicago*, 1936, *36:* 1225–1235.
9. LEMERE, F. Berger's α rhythm in organic lesions of the brain. *Brain*, 1937, *60:* 118–125.

THE EFFECTS OF ABLATION OF THE CORTICAL MOTOR FACE AREA IN MONKEYS*

HAROLD D. GREEN† AND A. EARL WALKER‡
Laboratory of Physiology, Yale University School of Medicine, New Haven

(Received April 12, 1938)

I. INTRODUCTION

THE PHYSIOLOGICAL significance of the cerebral cortex is not completely revealed by its responses to electrical stimulation, but the results of surgical ablation of these areas, when correlated with results of electrical stimulation give more complete insight into its function. In this paper the effects of surgical removal of the "motor face areas" will be presented and the results correlated with the electrical excitability of these regions (Walker and Green, 1938). The results offer a more complete physiological basis for localization of cerebral lesions.

II. HISTORICAL NOTE

Bouillaud introduced in 1830 the experimental approach to cerebral localization. His investigations of the effects of local cortical ablations in dogs on vocalization pointed to a localization of function within the cerebral cortex. Clinical observations (Broca, 1861–63), have been largely concerned with the speech defects from cortical destruction (Delavan, 1885), the less striking somatic phenomena being relegated to the background. With the advent of neurological surgery (Nancrede, 1888, and Lloyd and Deaver, 1888) observations on the effect of local ablations and extensive cortical resections (Dandy, 1933; Gardner, 1933) involving the face motor area have multiplied rapidly; experimental studies, however, have not been extensive.

Grünbaum and Sherrington (1903) described a crossed hemiparesis involving the lower facial musculature following ablation of the face area of a chimpanzee. In 1917, Leyton [Grünbaum] and Sherrington removed from a chimpanzee the cortex of the left precentral gyrus which upon electrical stimulation caused closure of the eyelids, but could detect no abnormality in the appearance of the animal. Even after removal of the comparable area of the right hemisphere, the eyelids were readily closed, although much less vigorously. Subsequent cortical stimulation did not produce movement of the eyelids. In another chimpanzee removal of the entire left precentral cortex, with the exception of a strip 1–2 mm. wide along the central sulcus, caused a right sided flaccid paralysis with bagging of the check. The nasal fold was less marked and the lips remained slightly open on the right side. "The tongue lay with its midline, especially just behind the tip, slightly to the left of the midline of the mouth," but no difference could be detected in the posture or movement of the forehead, eyebrows or upper eyelids. In a third chimpanzee ablation of the inferior part of the precentral convolution anterior to the electrically excitable cortex which yields movements of the face (corresponding to areas 6bα and 6bβ) caused no paralysis or other disturbance except "possibly slightly increased excitability." There was no change in vocalization.

Decorticate dogs have been studied by Goltz (1892), Zeliony (1913), and Rothmann (1910, 1923), decorticate cats by Dusser de Barenne (1919), Bard and Rioch (1937), and Hambourger (1937), and decorticate monkeys by Karplus and Kreidl (1914). Bard and

* This work was aided by a grant from the Research Funds, Yale University School of Medicine.

† Department of Physiology, School of Medicine, Western Reserve University.

‡ Fellow of the Rockefeller Foundation, 1935–36; now of the Division of Neurology and Neurosurgery, University of Chicago.

Rioch conclude "it is clear that the basal olfactory areas together with the associated ventral portion of the striatum and lower centers with which they are connected, namely, the hypothalamus, subthalamus and reticular substance of the brain stem, are capable of elaborate feeding reactions of a highly complicated type."

III. METHODS

For adequate study of the functions of the various areas and determination of the factors responsible for recovery, several types of experimental procedure were employed: unilateral and bilateral extirpations of areas 4 and 6 (face region), simultaneously or successively, and section of the peripheral hypoglossal nerve. The term, area 4c, will be used to refer to the face portion of area 4 only and area 6 (face) will be taken to include areas 6bα, 6bβ and the lower portion of area 6aα. The landmarks of these areas have already been described (Walker and Green, 1938). In all animals the extent of the lesion has been verified by complete serial section of the lesion and also of a generous amount of adjacent cortex. The ablated tissue was studied microscopically, in some cases in serial sections. In many instances the cortex was stimulated just prior to sacrifice to determine physiologically the completeness of the lesions. The type of operative procedure, duration of the period of observation and other pertinent data concerning the animals used in this investigation are included in Table I in which areas 4 and 6 refer to the face portion of these areas, *i.e.*, to areas 4c and 6a and b (lower part).

IV. RESULTS

1. Unilateral ablation of the entire face areas 4 and 6

Areas 4c and 6.—Following complete unilateral ablation of the motor and premotor face areas the muscles of the lips are completely paralyzed, the palpebral fissure is wider and closure of the eyelid weaker on the contralateral side. The buccal pouch on the paralyzed side becomes distended, and food, lodging between the teeth and cheek, falls from the buccal cavity. The body of the tongue lies in the midline, or slightly to the paralyzed side, with the distal third curled to the side of the lesion and the extreme tip at times curled underneath and towards the opposite side. Stimulation of the floor of the mouth on the paralyzed side causes vigorous rotation of the tongue to that side, but stimulation of the other side elicits little or no response. The ipsilateral half of the tongue seems to contribute to the movements to a far greater extent than the contralateral half. When the tongue is protruded it assumes an exaggeration of the resting position. A month after operation the palpebral fissures are equal and a considerable degree of facial movement has become apparent. After about three weeks the tongue can be rotated to the side of the lesion, but never as fully as to the contralateral side.

Experiment 1. Initial ablation of left face areas 4 and 6. Severe transient paresis of contralateral facial muscles and tongue. Macaca mulatta, A.6-62. Weight, 2700 gms.

First operation, January 5, 1936. Under sodium amytal anesthesia a left osteoplastic flap was reflected, the pia incised with the Bovie unit, and the cortex of areas 4 and 6 (face area) ablated by a subpial dissection.

Postoperative notes—2nd day. The animal was in good condition. The right palpebral fissure was slightly larger than the left, and there was a marked weakness of the right lower facial muscles. The body of the tongue lay in the midline but the tip curled to the left. Stimulation of the floor of the mouth on the right side resulted in vigorous rotation of the tongue to the right, whereas similar stimulation of the left side caused practically no movement. Vocalization was poor, but swallowing normal.

5th day. The reaction to pin prick on the right cheek and shoulder seemed slightly diminished. The masseters contracted equally well on the two sides. The jaw jerk was not

TABLE I

No.	Animal*	Operations	Inter operation interval	Total post-operative observation period	Terminal stimulation	Comment
33	M	Initial ablation: left areas 4 and 6; secondary ablation: right areas 4 and 6	5 mos.	11.5 mos.	Yes	
62†	M	As above; tertiary ablation, left inferior postcentral gyrus	1 mo. ½ mo.	8 wk.	Yes	Respiratory tracings made pre- and post-operatively
34	M	Ablation left areas 4 and 6		8 wk.		Died immediately following removal right areas 4 and 6
55	M	Same		16 days		Marchi degeneration
35	M	Ablation right area 6		4.5 mos.		Left cortex exposed previously; stimulation unsatisfactory
46	M	Ablation left area 6		14 days		Marchi degeneration
56	M	Ablation left area 4		14 days		Marchi degeneration
S.P. 16	B	Ablation left area 4		5 mos.	Yes	
S.P. 19	B	Ablation left area 4		2 mos.		
61†	M	Initial ablation: left and right areas 4; secondary ablation, left area 6	2 wks.	2 mos. + +	Yes	
32	M	Ablation left and right areas 4 and 6		8 days		Sacrificed on 8th postoperative day scalp infection
65†	M	Ablation left areas 4 and 6; section left hypoglossal nerve		4 wks.	Yes	
63†	M	Initial ablation, left area 6; secondary ablation, right area 6	2 wks.	6 wks. +	Yes	Respiratory tracings made pre- and post-operatively
70	M	Section left hypoglossal nerve		5 days		
71	M	Initial left hemidecortication; secondary right hemidecortication	6 wks.	7 wks.		
72	B	Same	2 mos.	2 mos.		

* M—monkey; B—baboon.

† Brief abstracts of the protocols of animals Nos. 62, 63, 61 and 65 are included in this paper as Experiments 1, 2, 3 and 4 respectively.

At the beginning of this investigation reliance was placed mainly on observation of the behavior of the animal in the cage—its cry, emotional expression and mastication. It soon became evident that these activities depended upon primitive mechanisms which cortical lesions affected only slightly. Further procedures therefore were introduced, touching with a blunt probe the outside of the cheek, the buccal mucous membrane, the tongue and the soft palate, comparing the complexity of the responses, on the paralyzed side with those of the normal side, or with those of the normal animal. These tests made possible the detection of abnormalities in the motor performance of the facial and lingual musculature which would otherwise have gone unnoticed. Observation of the animal's attempt to remove the irritating probe from the mouth or prevent its entrance was found to be particularly informative.

exaggerated. The left cheek moved vigorously when touched, but the right was immobile when similarly stimulated. Food remained in the right side of the mouth between the cheek and teeth but the food pouches were about equally filled.

6th day. The right palpebral fissure continued larger than the left and the right lower facial weakness was prominent. Part of the time the tongue lay in the midline and at other times slightly to the right of the midline, the tip curled always to the left and usually lay to left of the midline. Rotation of the tongue as described above was again noted. The left side of the tongue seemed to participate in this movement much more than the right. The temperature response to cooling and warming was the same on the two cheeks.

12th day. There was a slight movement of the right side of the face, but much weaker than the left. The weakness was much more apparent on volitional than on emotional grimacing. The tongue was rotated and deviated to the right much better than to the left. No dysphagia was present and vocalization was good.

21st day. Only a slight facial weakness was present. The body of the tongue was in the midline, with the distal third to the right of the midline, the extreme tip curled underneath and to the right. The tongue could be rotated and deviated to either side, but both movements were through a fuller range to the right.

27th day. The palpebral fissures were equal. The right side of the mouth moved fairly well both voluntarily and emotionally but movements were less marked than on the left. The tongue could be protruded but usually the distal third was slightly to the left with the extreme tip curled to the right. The animal vocalized well. On the 28th day following the first operation the "motor face" cortex was removed from the right hemisphere. The subsequent findings are presented in Section 2, p. 266 (see also Experiment 4, Section 5, p. 273).

Unilateral extirpation of area 4c. Removal of area 4*c* resulted in a marked paresis of the opposite lower facial musculature lasting from 8 days to over 5 weeks, and slight widening of the contralateral palpebral fissure. The longer paresis would appear to be more characteristic since the rapid recovery occurred in an animal in which a fringe of electrically excitable area 4*c* cortex remained. The range of lingual movement was markedly diminished, particularly when the animal attempted to execute complicated motions with the tongue. In its resting position the body of the tongue lay approximately in the midline. Rotation of the tongue to the ipsilateral side was impaired. Later (5–6 weeks) this function was partially recovered.

Unilateral extirpation of face area 6. Ablation of the lower part of areas 6*a*α, 6*b*α and 6*b*β produced a transient paresis of the contralateral lower facial musculature but no inequality of the palpebral fissures. The tongue usually lay in the midline and in response to stroking the floor of the mouth deviated and rotated only to the side opposite the lesion. In contrast with the sequelae of area 4 lesions these signs disappeared rapidly. By one week the tongue could be moved equally well to either side and the paresis of the lip was almost gone.

Experiment 2. Ablation of left area 6 (face); transient contralateral facial weakness and lingual paresis. Macaca mulatta A.6-63. Weight 2800 gms.

First operation. June 15, 1936. Under sodium amytal anesthesia a left osteoplastic craniotomy was performed. Using subpial dissection, area 6 (face) was ablated.

Postoperation notes—2nd day. The right corner of the mouth drooped slightly but could be retracted. The masseters contracted strongly; the tongue lay slightly to the left of the midline, and could be rotated and deviated fully to the right but poorly to the left.

5th day. The masseters contracted equally on both sides. The slight right lower facial weakness was still evident. The tongue lay in the midline and could be rotated and deviated equally well to either side. The voice was normal.

12th day. There was a slight lag in retracting the right angle of the mouth, but otherwise no abnormalities were apparent in the cranial nerves. On the thirteenth postoperative day, the right face area 6 was removed (see p. 270).

2. Bilateral ablation of the motor and premotor areas

Practically complete loss of motion of the lower facial muscles and of the distal half of the tongue occurred initially. The pouches remained filled; food clung between the teeth and the cheeks and spilled from the buccal cavity. The voice was a feeble chirp or low pitched and husky; the characteristic noisy chatter and variation of intonation were absent. The bite was often weak or more often was normal. Slight movement of the angles of the mouth and rotation of the tongue could be elicited within about three weeks, by which time also the distention of the pouches had become less prominent, but complete recovery of movement did not occur. Stimulation of the posterior wall of the pharynx elicited a contraction of the posterior half of the tongue rarely sufficient to protrude the tip past the lower teeth. Only weak contractions of the intrinsic muscles of the distal third of the tongue could be seen.

Experiment 1 (continued). Secondary ablation of right face areas 4 and 6; severe bilateral facial and lingual paresis with slow recovery. Tertiary ablation of inferior portion of left postcentral cortex; practically no change in motor status (continued from p. 265).

Second operation. February 2, 1936. Twenty-eight days after ablation of the left face areas 4 and 6 the animal was anesthetized with sodium amytal and a right osteoplastic flap reflected. The central, inferior precentral and sylvian sulci were opened and the cortex lying between them removed in one piece. The lesion extended superiorly to the vein marking the upper border of the face area.

Postoperative notes. Neither hand was used well and food fell often from the hands during feeding. The mouth was opened and closed readily. The response to pin prick was equal on the two sides of the face. The right cheek retracted slightly when the right side of the buccal mucous membrane was irritated, but no response occurred on the left side to such stimuli. The tongue lay flat in the mouth; only its posterior half moved. Food hung from the lips and corners of the mouth. No jaw jerk could be elicited. The voice was low pitched and feeble.

29th day. The right palpebral fissure was larger than the left. Both eyes could be closed strongly. The only lingual movement was elevation of the posterior half of the tongue.

30th day. The grimacing characteristic of the macaque monkey was not seen and the lower facial muscles were immobile, except for a slight retraction of the right cheek when the buccal mucous membrane was irritated. The masseters contracted forcibly on both sides. The animal made no attempt to swallow when food or water was placed in its mouth. Accordingly 200 cc. of milk were given by stomach tube. The palpebral fissures were equal.

32nd day. The movements of the right side of the face were increased in range and strength. The voice was stronger but still low pitched and lacked the usual range of intonation. The palpebral fissures were equal and the eyelids closed vigorously.

37th day. The right cheek could be retracted slightly but retraction of the left cheek was still absent. The tongue lay in the midline; the only movement observed was elevation of its body.

40th day. The left food pouch was full, the right empty. The tongue was protruded over the teeth, but was not rotated.

Third operation. February 17, 1936. On the 15th day following the second operation the animal was anesthetized with sodium amytal, the left bone flap reelevated, and the inferior portion of the postcentral convolution ablated.

47th day. The left food pouch which had been consistently dilated was now about the same size as the right. There was perhaps slightly increased tone in the right food pouch, when tested with the examining probe. The right corner of the mouth could be retracted but the left remained immobile. There was about 10° rotation of the tongue to the left with slight curvature of the body to the right.

49th day. Both angles of the mouth could be retracted about 2–3 mm. upward and backward. The animal still had difficulty keeping food in its mouth. The cry remained weak. There were gross movements only in the posterior and middle thirds of the tongue with only slight changes in contour of the distal third. The tongue could be rotated about 20–30° to either side and protruded about 2 mm. over the teeth.

57th day. The findings were approximately the same as previously. Only the posterior one-third of the tongue could be rotated. Slight narrowing of the distal third of the tongue occurred during elicitation of the gag reflex.

Terminal stimulation. March 2, 1936. On the 13th day after the third operation the animal was anesthetized with ether and the operative sites on the cortex of each hemisphere

FIG. 1. Photomicrograph of a serial section through the cortex of the right face area in Experiment 1, including the central sulcus and the tissue remaining immediately anteriorly to this sulcus. The section is taken through a point in the cortex, marked with India ink, which yielded retraction of the left angle of the mouth and slow deviation of the tongue to the left at the terminal stimulation experiment.

reexposed. No responses could be obtained upon stimulation of the cortical face area on the left side, but on the right, from a point on the central sulcus, retraction of the left angle of the mouth and slow deviation of the tongue to the left were produced (see Fig. 1). Another point below the inferior precentral sulcus gave rise to rhythmical movements of the tongue and jaw.

Postmortem examination. Body weight 2400 gms; brain weight 65 gms. Gross examination of the body showed no abnormalities. In the right hemisphere the ablation damaged the inferior portion of area 3. The anterior inferior part of the ablation was bounded by granular frontal cortex except for the most inferior sections in which agranular frontal cortex was present on the anterior margin of the lesion. Hence practically all of areas 4c and 6 (face) had been removed. In the left hemisphere the lesion extended superiorly along the posterior lip of the inferior limb of the precentral sulcus damaging only superficially the granular cortex anterior to the latter sulcus. It extended posteriorly to the central sulcus, crossed it and passed just below the inferior tip of the intraparietal sulcus. The posterior margin of the ablation was bounded by area 2 cortex; area 7 and the cortex of the island of Reil appeared not to have been damaged (Fig. 2).

Bilateral ablation of area 4. Immediately following a bilateral extirpation of area 4 the range of movement of the muscles of the lower half of the face was markedly diminished, although sucking movements could be obtained by

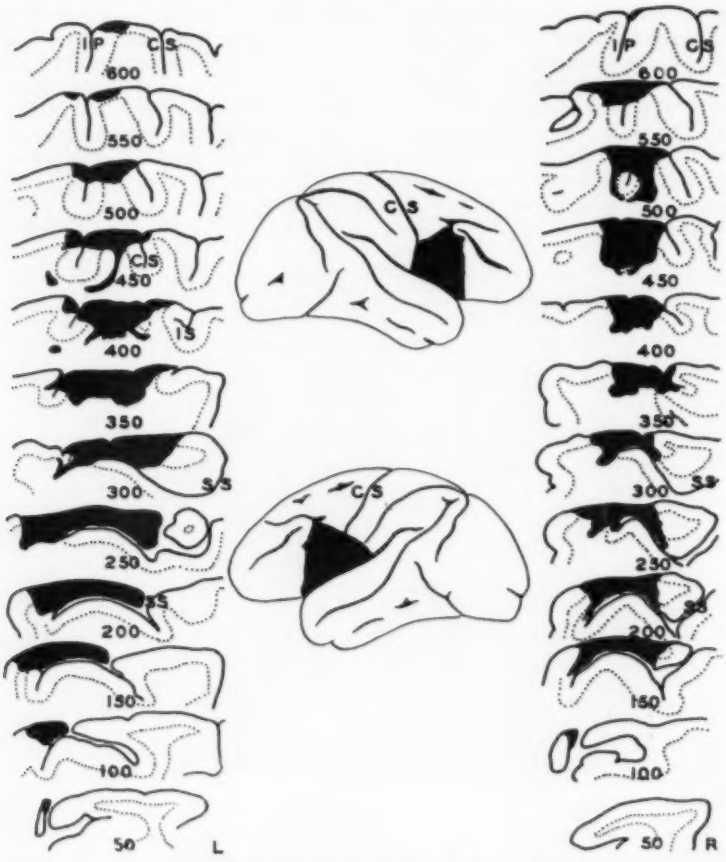


FIG. 2. Drawings showing the external configuration and the extent of the cortical ablation observed in the serial sections of the face area and immediately surrounding regions of the cortex in Experiment 1. In this and the similar figures to follow: the solid black indicates the extent of the destruction of the cortex, the serial sections are numbered from the ventral to the dorsal section, L = sections from the left cortex, R = sections from the right cortex, IP = intraparietal sulcus, SS = lateral (Sylvian) sulcus, and AC or SA = anterior subcentral sulcus.

stroking the dorsum of the tongue. Vigorous stimulation of the posterior wall of the pharynx elicited slight humping of the posterior part with forward and backward movement but no evidence of active contraction in the anterior two thirds of the tongue. After approximately $1\frac{1}{2}$ months slight rotation of the tongue to either side could be obtained and this movement increased in range until about 60° rotation was present, but it was never possible to obtain significant deviation of the tongue. Although, after two months, slight contractions could be observed in the distal half, resulting in narrowing of the tip, the tongue was poorly protruded.

Experiment 3. Simultaneous bilateral ablation of area 4c; severe bilateral facial and lingual paresis. Secondary ablation of left area 6 (face); slight increase in right facial and lingual paresis. Macaca mulatta. A. 6-61. Weight 2700 gms.

First operation. May 29, 1936. Under nembutal anesthesia, a bilateral osteoplastic craniotomy was performed. The pia was incised with the Bovie unit and area 4c on each side ablated.

Postoperative notes—1st day. The animal was in good condition. Both corners of the mouth retracted feebly when the animal attempted to bite. Eye movements were normal. The bite was vigorous, the cry high pitched. The tongue could be moved forward and backward, but lateral deviation was not observed.

6th day. There appeared to be some excessive salivation, perhaps due to inability to prevent the saliva from drooling from the corner of the mouth. The reactions of the orbital and ocular muscles were normal.

9th day. Food was constantly present between the teeth and cheeks, and the mouth appeared more unkempt than normal for a monkey.

13th day. The weakness of cheek muscles was still prominent but the range of retraction of the lips was increasing. The tongue lay in the midline and was moved forward, backward and sideways slightly. Its posterior half could be elevated. Most of the movements were made with the body of the tongue, the tip remaining immobile. The jaw jerk was not exaggerated.

28th day. The tongue moved forward and backward as a unit while the tip remained stationary, thus forward movements resulted in doubling the tongue over itself. The tip was not moved out over the lower teeth and no rotation was present.

44th day. Facial and labial, and biting and crying movements were feeble. The tongue could be rotated 20–30° to each side. A swallowing reflex could be elicited by stroking the posterior wall of the pharynx but the associated tongue movement was limited to its posterior part.

56th day. Both sides of the mouth retracted slightly, the left better than the right when the animal was excited or cried, but the reverse was true when the movement was volitional. Sucking movements were made with the lips and tongue when the tongue was stroked. The food pouches were empty. Contraction of the intrinsic muscles of the distal third of the tongue with slight narrowing was observed for the first time. The tongue could be rotated about 60° to the left and 45° to the right. The tongue was extended in the midline 2–3 mm. over the lower teeth.

Second operation. July 24, 1936. On the sixtieth day after the first operation the animal was anesthetized with ether and the left face area reexposed. Stimulation of remaining cortex yielded only slight retraction of the right angle of the mouth from a point high along the central sulcus in the face area and rhythmical movements of the tongue from along the inferior precentral sulcus. The cortex lying anterior to the previous ablation, inferior to the precentral sulcus, and extending to the sylvian sulcus was ablated by blunt dissection, the dura replaced but not sutured, and the bone flap replaced.

57th day. When the animal cried, the left side of the face was retracted sufficiently to expose the molars, the right side enough to expose the incisors. Stroking the cheeks resulted in better pursing movements on the left. The left palpebral fissure was slightly larger than the right. Stroking the tongue resulted in pursing of both lips, narrowing of the distal third of the tongue and elevation of the jaw. The tongue could not be deviated nor protruded to the teeth, but could be rotated about 30° to the right and only about 10° to the left, and could not be deviated. There was increased resistance to opening the jaw.

58th day. The palpebral fissures were equal. The lips moved to a greater extent on the left than on the right in response to both excitement and stroking the cheek. The tongue rotated about 15° to the left but none to the right.

61st day. The tongue rotated to the right about 20° and to the left 5°. No movements could be elicited in the tip of the tongue.

65th day. Both cheeks could be retracted about 2–3 mm. The posterior half of the tongue rotated about 20° to either side upon stimulation of the floor of the mouth. When the gag reflex was elicited the tongue was pushed forward to the teeth. No deviation of the tongue but slight narrowing of the distal tip was observed.

Terminal stimulation. On the 9th day following the second operation the animal was sacrificed under deep anesthesia. Because of extensive adhesions it was deemed unwise to attempt to remove the dura over the left cerebral cortex. The cortex on the right side was exposed and stimulated with 60-cycle alternating current. Complex rhythmical jaw and tongue movements were obtained from the remaining cortex of area 6. Stimulation of the anterior margin of the central sulcus in the upper part of the face area produced retrac-

tion of the left angle of the mouth and deviation of the tongue to the left. Points a short distance from this anteriorly and posteriorly gave the same response, but with a longer latency (spread ?).

Postmortem examination. Body weight 2700 gms.; brain weight 75 gms. Gross examination of the body showed no abnormalities. In the right hemisphere the lesions involved all of area 4c, except a strip along the anterior margin of the central fissure. It damaged the adjacent areas 6aα, 6bβ and 3 but did not involve the frontal granular cortex or the postcentral convolution. In the left hemisphere the lesion almost completely removed areas 4c and 6aα, 6bα and 6bβ from the inferior part of the precentral convolution and damaged the cortex of the frontal granular region. Two softenings, one in the postcentral convolution and a second in the temporal region, complicated the ablation (Fig. 3).

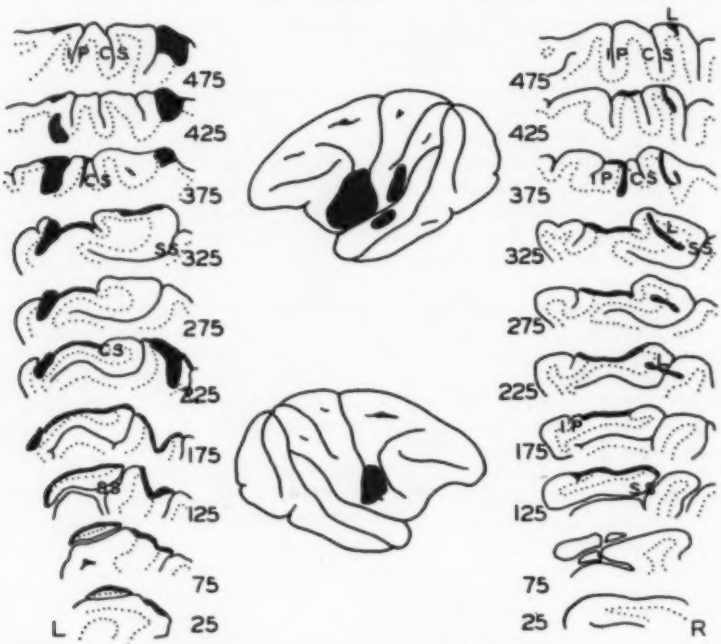


FIG. 3. Drawings showing the external configuration and the extent of the cortical ablation in Experiment 3. See Fig. 2 for legends. L, incision made in right cortex toward the end of the terminal experiment.

Bilateral ablation of area 6. Initially there was paresis of the lips and reduction of the range of lingual movement. Within one week the movement of the cheek and lingual muscles greatly increased and contractions were observed in the intrinsic tongue muscles. By the end of four weeks it was difficult to detect any signs of paralysis.

Experiment 2 continued. Secondary ablation of right area 6 (face); transient bilateral facial and lingual paresis. (Continued from p. 266.)

Second operation. June 28, 1936. On the 13th day after ablation of the left area 6 (face) a right osteoplastic craniotomy was performed under sodium amytal anesthesia and area 6 (face) removed by subpial dissection.

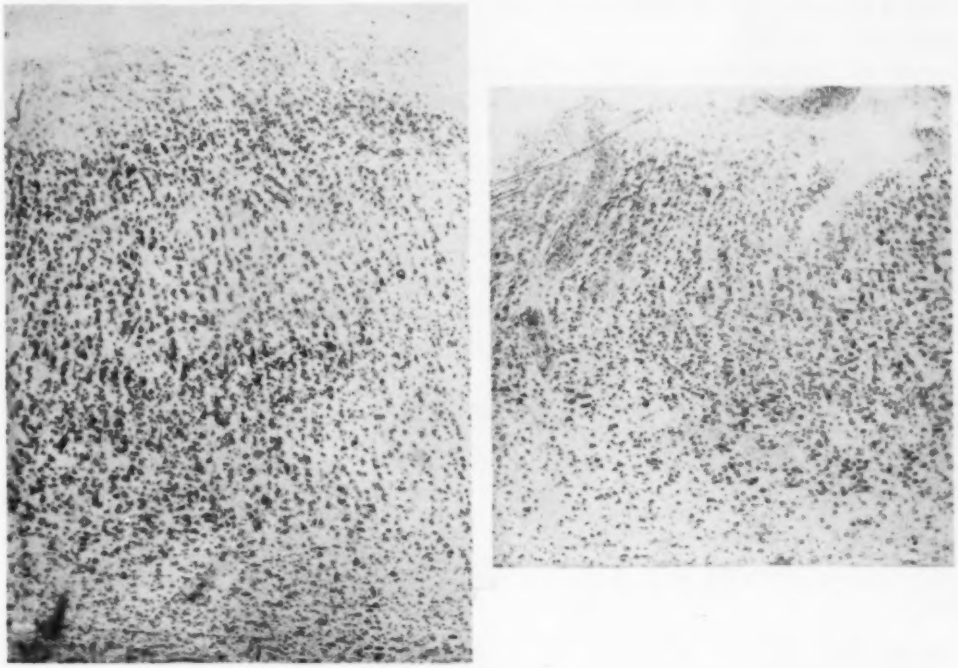
14th day. There was a slight bilateral facial weakness. The tongue lay in the midline but was not rotated well to either side.

17th day. The masseters contracted well. The jaw jerk was not exaggerated. The left side of the face lagged slightly behind the right when the corners of the mouth were retracted. Vocalization and swallowing were normal.

21st day. No facial weakness could be detected. The tongue could be protruded well past the teeth, rotation was limited to 45° to either side and deviation was slightly impaired to both sides. The intrinsic muscles of the tongue contracted vigorously.

37th day. There was no facial or lingual weakness. The animal appeared normal.

Terminal stimulation experiment. On the 32nd day after the second operation the animal was anesthetized with ether and the cortex stimulated. Typical sustained responses were obtained from the remaining cortex of area 4 on both sides. On the left side rhythmical movements of the tongue and jaws were elicited from the posterior margin of the ablation (see Fig. 4).



A B

FIG. 4. Photomicrographs of two serial sections of the cortex in Experiment 2. In this experiment an attempt was made to remove area 6 (face) bilaterally. On terminal stimulation rhythmic movements of the tongue were obtained from excitation near the left anterior subcentral sulcus. Here transitional cortex (6bα and 3b) with large cells in the lower portion of the third and upper parts of the fifth layer were found (Section A). On the opposite side no such response could be obtained and histologically there was no semblance of area 6bα tissue (Section B).

Postmortem examination. Gross examination of the body showed no abnormalities. In the right hemisphere the lesion had almost entirely removed area 6, damaged a small part of the lower portion of area 3, and undermined a small portion of the granular frontal cortex. On the left side the lesion had entirely spared area 3, removed most of the lower part of area 6, and slightly damaged the frontal granular cortex (see Fig. 5).

3. Observations peculiar to serial ablations of the cortex

When the ablations of the motor face areas are carried out in sequence the paralysis resulting from removal of the second area is more than double that resulting from unilateral extirpation. There is considerable recovery in

the retraction of the angle of the mouth opposite the initial lesion after about two months. Immediately after the second operation the movements of this cheek are greatly impaired, but recover more rapidly than those of the newly paralyzed cheek. About two months after the initial lesion, the tongue can be rotated normally to the contralateral side and has recovered about 45–60° motion towards the side of the lesion; but immediately after the second operation this recovered movement to the ipsilateral side is markedly decreased and never completely recovered (see Experiment 1, Section 1a, p. 263; and Section 2, p. 266).

While removal of area 4c subsequent to a bilateral extirpation of area 6 (face) would be of interest its particular significance was not considered im-

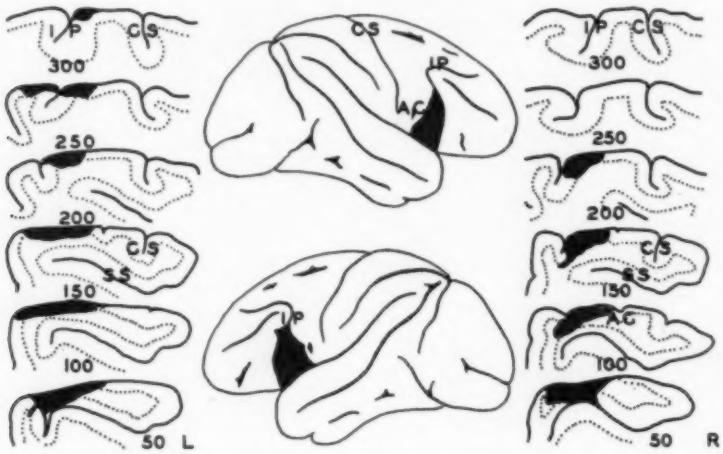


FIG. 5. Drawings showing the external configuration and extent of the cortical ablation in Experiment 2. See Fig. 2 for legends.

portant, because of the normally greater degree of paralysis following the former operation compared with the latter. However, the effect of removal of an area 6 (face) subsequent to a bilateral removal of area 4c should give a clue to the function of area 6 (face), particularly the part the latter might play in recovery. In one animal (Experiment 3, Section 2, p. 268) that recovered motility in the lips contralateral to the second ablation was considerably decreased, rotation of the tongue was diminished, and the activity of the intrinsic muscles of the distal third was impaired. This difficulty was not as permanent as that seen in complete bilateral ablations of the motor face areas perhaps explicable by ipsilateral innervation from the remaining area 6 (face).

4. Generalizations common to all lesions

A number of findings, mainly negative, were common to most lesions. In many animals the bite was weak for the first few hours postoperatively but after the second day no reduction in strength could be detected. No defi-

nite deviation of the jaw was noted and the two masseters always contracted equally. Dysphagia was never apparent. A definite jaw jerk was present only in one monkey which had had a complete bilateral decortication. In a few animals slight paresis of the arms was seen, probably due to coincidental damage to the suprajacent arm area. Although movements of the ears cannot be judged accurately because of the operative procedures no loss of motion was apparent. Transient diminution of sensation about the face appeared to be present in one animal.

5. *Ipsilateral representation*

In our previous paper it was demonstrated that movements of the tongue can still be produced by cortical stimulation of the contralateral face area after the hypoglossal nerve has been sectioned, and that in the normal animal rotation and deviation to either side can frequently be obtained by stimulation of a single area. These findings suggest that each half of the tongue is bilaterally represented in the cerebral cortex, or in other words, that there is ipsilateral cortical representation of the lingual muscles. In order to test this assumption further in a chronic experiment, the entire face area was removed from one hemisphere and the hypoglossal nerve sectioned on the same side. In this preparation lingual movements had to originate either subcortically or in the ipsilateral hemisphere.

Experiment 4. Simultaneous ablation of the entire left face area and section of the left hypoglossal nerve; right facial paresis and severe impairment of lingual movement. Macaca mulatta A.6-65. Weight 2400 gms.

First operation. July 8, 1936. Under sodium amytal anesthesia a left osteoplastic flap was reflected. The pia was incised with the Bovie unit and areas 4c and 6 of the face region were extirpated. Especial care was exercised to remove all area 4 tissue from along the central sulcus. At the same time the left hypoglossal nerve was sectioned below the ramus of the jaw.

Postoperative notes—3rd day. The right side of the cheek was completely immobile except for slight retraction in emotional crying. The palpebral fissures were equal but a little more firmly closed on the left. The masseters contracted equally and strongly. The tongue lay motionless in the floor of the mouth. When the swallowing reflex was elicited the tongue elevated only posteriorly and slightly in its middle third. Considerable food was present in the buccal cavity—perhaps an indication of dysphagia.

6th day. There was no real change in the status of the facial and lingual musculature.

18th day. The palpebral fissures were equal. The right facial muscles moved feebly. The tongue at rest was slightly curved to the right side with the tip definitely to the right. The tongue could be rotated and deviated to the right fairly well but poorly to the left. There was no active movement of the left side of the tongue. It could be protruded past the teeth although usually somewhat to the right of the midline.

21st day. There was poor volitional retraction of the right side of the mouth but it was strong under excitement, although less than on the left. At rest the tongue lay in the midline with the tip slightly curved to the right. When the tongue was stroked there was slight closing of the jaw and a pursing movement of the lips. The tongue could be rotated about 60° to the right and 20° to the left. Deviation of the tongue was observed to the right only.

26th day. The right corner of the mouth could be retracted feebly, and closure of the lips on the right side was weak. Stroking the floor of the mouth produced deviation of the tongue so that the tip was placed over the right lower incisor, but no deviation could be obtained to the left. The body of the tongue could be rotated about 45° to either side and the distal third to the right about 60° but not more than 20° to the left. Stroking the pos-

terior wall of the pharynx produced a gag reflex, with the tongue protruded over the teeth and slightly to the left of the midline.

Terminal stimulation experiment. On the 26th day after the operation the animal was anesthetized with ether and the cerebral cortex bilaterally exposed. When the left cortex was stimulated, the only response in the face was obtained from a point on the central sulcus producing twitching of the right cheek and eyelids. Stimulation of the right cortex gave rise to strong responses in the oral and lingual musculature, both complex and discrete movements being observed.

Postmortem examination. Body weight, 2200 gms.; brain weight, 73 gms. Gross examination of the body showed no abnormalities. The cortex of the *right* hemisphere appeared quite normal except for a few ink marks made at the time of stimulation. The outline of the excitable area with a liminal stimulus, indicated with ink dots, corresponded closely with the cytoarchitectural outline of area 4, but the latter was slightly smaller than the

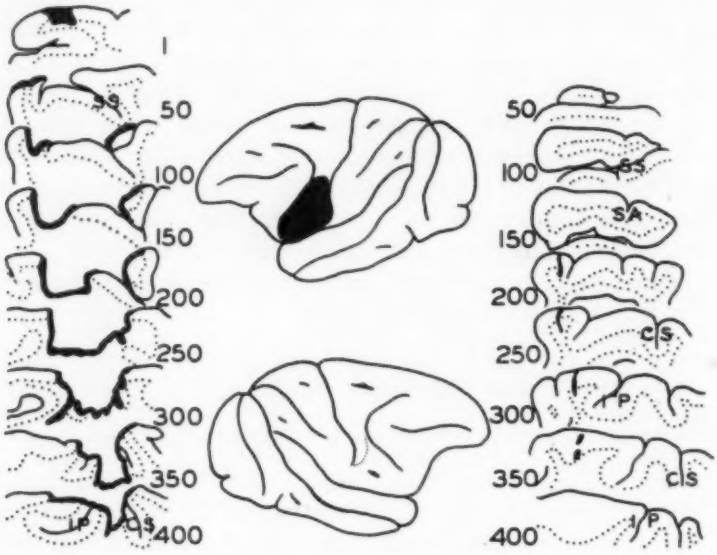


FIG. 6. Drawings showing the external configuration and extent of the cortical ablation in Experiment 4. See Fig. 2 for legends.

former, the difference being about 1 mm. throughout. The ablation of the *left* hemisphere had removed all the cortex of the motor and premotor region of the face area and damaged the adjacent cortex of the postcentral and frontal granular regions. There was no evidence of cortex of types 6aα, 6bβ, 6bα or 4c in the lower face area (see Fig. 6).

In order better to evaluate the above experiment, one hypoglossal nerve (left) was sectioned in another animal, the cortex being preserved intact. Following the operation the tongue lay about 2–3 mm. to the contralateral side. Deviation of the tongue to the contralateral side often associated with the angulation at the junction of the distal and middle thirds was possible, whereas the animal was quite unable to deviate the tongue to the ipsilateral side. Similarly rotation, evidenced by depression or elevation of the right half of the tongue, was possible to about 60° to the contralateral and only 5–10° to the ipsilateral side. The tongue could be protruded past the teeth usually to the contralateral side of the midline.

V. Discussion

Hughlings Jackson has emphasized that lesions of the cerebral cortex manifest themselves either by negative (paralyses) or positive (release) phenomena in either the somatic or autonomic spheres. Disorders of the former sphere, seriously impeding the activities of the individual, are more striking and impressive than those of the latter, and only recently have been reëmphasized.

Motor disturbances (*paralyses*). Stimulation of the monkey's motor face cortex (Walker and Green, 1938) yields: (i) contractions of the lower facial musculature, limited almost solely to the contralateral side; (ii) contractions of both contra- and ipsilateral lingual musculature; (iii) occasionally and almost always bilaterally, movements of pharyngeal, laryngeal or upper facial muscles. It would be expected then that the negative phenomena resulting from unilateral ablation of these areas would not be a general paralysis but would show certain predilections; this indeed has been strikingly true. The most conspicuous weakness is that of the lower facial musculature; impairment is less pronounced in the tongue, and least of all in the pharyngeal, laryngeal and upper facial muscles. Recovery takes place in the reverse order, so that when little or no abnormality of the lingual musculature can be detected a lower facial weakness is still apparent. Evidence from the results of capsular lesions or cortical resections involving the face motor area (Grinker, 1934; Wechsler, 1935; Dandy, 1933; Gardner, 1933) indicates a similar relationship in the human being. If the motor face area be removed bilaterally the lingual as well as the lower facial movements are much impoverished, and those of the pharyngeal and laryngeal to a considerable extent impaired, while those of the upper facial muscles are but little depressed. From these observations during stimulations and after ablations one may conclude that, in the monkey, the lower facial and lingual musculatures are extensively, the pharyngeal and laryngeal considerably, and the upper facial musculature but little represented in the cerebral cortex.

A comparison of the results of stimulation both before and after section of the contralateral hypoglossal nerve, with those of unilateral, and bilateral removal of the motor face areas, and with those of ablation of one motor face area plus section of the ipsilateral hypoglossal nerve, leads one to the conclusion that in the monkey, although the lower facial musculature has largely a unilateral cortical representation, the lingual, laryngeal and pharyngeal muscles have extensive bilateral representation and that even the slight cortical representation of the upper facial musculature is largely bilateral. This last conclusion is in keeping with Leyton and Sherrington's (1917) observation in the chimpanzee.

The clinical manifestations of lingual involvement by a unilateral cortical, subcortical, or peripheral nerve lesion especially the deviation to the paralyzed side and poverty of movement, are all described in textbooks (Grinker, 1934; Wechsler, 1935; Jelliffe and White, 1935). Observations on experimental animals are necessarily incomplete. Monkeys with unilateral lesions

of the face areas 4, or 4 and 6 show the deviation of the tongue to the paralyzed side, and the poverty of movement characteristic of the clinical lesion. In addition, markedly impaired rotation of the tongue to the normal side was a characteristic feature of the unilateral preparations, although such a phenomenon does not appear to have been described clinically.

Although rhythmic movements are consistently obtained from electrical stimulation of 6$b\alpha$, it is unlikely that their rhythmic nature is elaborated in the cortex since: (i) Magoun, Ranson and Fisher (1933) were able to obtain the similar rhythmic movements (lapping and mastication) from stimulation of the white matter of the internal capsule and basis pedunculi, and (ii) animals with bilateral ablation of the motor face areas and even complete decortications possess these movements sufficiently well to chew food and in some cases to east unassisted.

Autonomic disturbances. In a previous paper (Walker and Green, 1938) respiratory changes and salivation were described as a result of stimulation of the premotor face area. Respiratory tracings have been made pre- and postoperatively from two animals, but no alterations were detectable. Following bilateral ablation of the motor face area drooling of saliva from the corners of the mouth is present for over a week. Whether this represents true sialorrhea, or is merely the result of inability to swallow is impossible to say in the absence of quantitative determinations of salivary flow. Skin temperature measurements of the face and extremities were recorded in one animal (Experiment 1, p. 265) after unilateral ablation of the face motor and premotor areas but no difference could be detected during or after change of the environmental temperature. The temperature of both sides of the face followed closely the rectal temperature.

Release phenomena. It is difficult to evaluate the rôle of "release" in the signs present following cortical ablations. Spasticity which is the outstanding phenomena in the extremities after lesions of the motor and premotor cortex, is difficult to determine in facial and lingual muscles. It is perhaps suggestive that the food pouches, moderately filled after eating in the normal animal, are, for a few days after a unilateral area 4, or 4 and 6 ablation, abnormally distended on the contralateral side, but are rarely filled to any extent upon recovery from the extirpation. In Experiment 1 (p. 266) approximately three weeks after the completion of a serial bilateral extirpation of areas 4 and 6, the pouch opposite the second operation had returned to about the same size as its fellow. When tested more resistance, however, was offered to the entrance of the examining probe on the side opposite the first operation. On the other hand, a similar test made on a hemidecorticate monkey six weeks after operation failed to show any difference in the resistance on the two sides. Increased resistance to opening the jaw has been noticed in three animals, one with bilateral ablation of area 4 (Experiment 3) and two with bilateral areas 4 and 6 lesions (No. 33, and Experiment 1), but in none of these was a definite jaw jerk elicited. The two completely decorticate animals showed both increased resistance to opening the jaw and the presence of a definite jaw jerk.

The forced laughter and crying which characterize bilateral supranuclear bulbar lesions in man, producing the pseudobulbar syndrome, have been lacking in our animals with double ablations of the cortical motor face areas. It is not improbable that such emotional disturbances are the result of lesions of the striatum or of the fibers from the latter rather than of the cerebral cortex. We have, however, noted frequently that an animal may respond, when excited, with a facial or lingual movement which apparently cannot be carried out volitionally. These responses are non-specific, violent, and poorly adjusted to the desired end, *i.e.*, both sides of the mouth may be fully retracted by an animal, in which both face areas have been removed, if a painful stimulus is applied to a limb, or the animal is angered, although such movements are never seen in the normal behavior of the animal, nor can they be elicited by stroking the cheek or placing an object between the teeth. Similarly gentle stroking of the tongue or back of the throat in bilateral 4, or 4 and 6 preparations, fails to cause the normal protrusion of the dorsum of the tongue towards the irritating object, and it frequently fails to elicit any movement of the body of the tongue; but if the posterior pharyngeal wall is stimulated vigorously with the probe, producing a gag reflex, the entire length of the tongue may be protruded in the midline. These emotional or reflex movements occurring in an otherwise paralyzed organ, we believe, originate at subcortical levels. In support of this contention is the occurrence of essentially similar movements in completely decorticated animals. This dissociation of volitional and emotional facial responses is a fact well known clinically. It is even true that the paretic side may react before and to a greater extent than the normal side of the face.

Regions responsible for recovery after cortical lesions. Many investigators have discussed the factors responsible for "taking over control" following cortical ablations. The present study contributes the following evidence to the solution of this problem.

a. Remaining homolateral tissue of the motor or premotor area. It has been evident that the recovery was more rapid and complete in animals in which the removal of the motor and premotor areas was incomplete than in those in which the ablation included all of areas 4c and 6 (face). Animal No. 33 showed an unusual degree of recovery after a bilateral area 4c and 6 (face) ablation. At the time of sacrifice a considerable amount of electrically excitable cortical tissue was demonstrated, and histologically a part of 4c was spared. The responses to stimulation were essentially the same as those which the animal showed in the face and tongue in the clinical examination. In later experiments in which especial care was taken to make the lesions complete, recovery was slow, and stimulation of the cortex at the time of sacrifice rarely elicited a response. After bilateral ablation of area 4c, subsequent removal of area 6 intensifies the paralysis on the contralateral side.

b. Ipsilateral representation in residual opposite motor or premotor area. The evidence favoring ipsilateral cortical representation particularly that of the tongue, has been reviewed above (p. 273). Unquestionably this factor

plays a large part in the recovery of function after a unilateral ablation. Fulton and Dusser de Barenne (1933) have emphasized the importance of the ipsilateral representation of the tail, and Fulton and Keller (1932) and Bucy and Fulton (1933) that of the extremities. Foerster (1936) found in man that even skilled movements of the distal portions of the extremities might be regained after ablation of the contralateral motor cortex, but these movements were always associated with the same movement in the normal extremity. He concluded that they were due to ipsilateral innervation from the intact motor cortex. Evidence of ipsilateral representation of the extremities in the motor and premotor areas has also been furnished by the studies of Marchi degeneration in the spinal cord and of the degeneration of boutons of the spinal terminations of the cortical projections (Kennard, 1935; Hoff and Hoff, 1934; and E. C. Hoff, 1935). Ogden and Franz (1918) concluded that removal of the second motor area did not diminish the motility recovered as a result of forced usage in an extremity paralyzed by extirpation of one motor area.

c. Sensory cortex. It has been suggested that, since the postcentral convolution is a source of extrapyramidal fibers, it may play a part in the recovery of function after lesions of the motor areas. In one experiment following a bilateral motor and premotor ablation the postcentral sensory cortex was removed. No further impairment of cheek or lingual movement was observed after this procedure (Experiment 1).

d. Subcortical centers. Subcortical centers must play a considerable part in recovery of function since in Experiment 1 the terminal stimulation of the cortex failed to elicit most of the movements observed in the clinical examination, and the postmortem microscopical examination showed virtually complete ablation of the motor areas. More direct evidence is presented by the observations made on two animals following serial bilateral hemidecortications. About one month after the left hemidecortication and 3 days after the decortication of the right hemisphere slight retraction of the right cheek could be elicited by stroking the hairs of the face, and stroking the dorsum of the tongue caused slight rotation of the tongue towards the probe, more marked towards the left and associated with depression of the jaw and contraction of the cheek muscles. No movements could be elicited from the left cheek.

A large part of any recovery must be due to the subcortical structures. Certainly there is good reason to expect that the emotional responses may originate subcortically since Ranson (1937) has shown that they can be induced both in a normal and in a decorticated animal by stimulating the hypothalamus, and Bard (1928) has shown their spontaneous origin in decorticated animals, thus proving the presence of motor projection pathways from this region independently of the cortical projections. The preservation of the ability to close its eyes in the case of Leyton and Sherrington's (1917) chimpanzee, the considerable activity of the decorticated animals, and especially the marked recovery of movements of the face and extremities of Gardner's (1933) patient with a hemidecortication, all point to the same conclusion. In

addition it is difficult to explain the motor activity observed in some of our animals with complete bilateral extirpations of the motor and premotor areas (in which terminal stimulation did not yield the responses seen during the period of observation) unless one admits some subcortical activity.

VI. Summary

1. The clinical pictures of monkeys with unilateral or bilateral ablation of area 4c, or the lower part of 6aα, 6bα and 6bβ, or both are described.

2. From these observations plus those of the stimulation experiments (Walker and Green, 1938) it is concluded that: (a) Area 4 contains the direct cortical projections to the labial muscles, the orbicularis oculi, the buccal food pouches, and to the intrinsic muscles of the tongue; (b) Area 6aα (face) probably normally influences the activity of area 4c, but has itself few direct motor projections; (c) Area 6bα possesses independent projections which are mainly concerned with gross and frequently rhythmic movements, particularly of the tongue, functions which may be in part carried out by area 4, but more especially by subcortical structures; (d) The projections from area 6bβ are likewise independent of those of area 4 and serve to modify the activity of the respiratory center.

3. The lower facial musculature (lips and buccal pouch) is represented almost solely in the contralateral cortex, while the upper facial, lingual, pharyngeal and laryngeal muscles are to a considerable extent bilaterally represented

4. Despite the bilateral representation of the lingual musculature, deviation and rotation of the organ towards a particular side are primarily controlled by a single area 4c, that of the homolateral hemisphere.

5. In the monkey the control of these various muscles is encephalized in descending order as follows: almost completely—lower facial (lips and buccal pouch) and lingual muscles, less marked—laryngeal and pharyngeal muscles, and least the upper facial muscles.

6. The factors responsible for recovery of motility after ablation of the cortical face motor and premotor area are, in order of importance: (a) remaining ipsilateral cortex of the motor or premotor face area; (b) contralateral motor and premotor cortex of the face region; (c) subcortical structures; (d) other cortical areas, sensory, prefrontal, etc.

The authors wish to express their appreciation to Professor J. F. Fulton for his many helpful suggestions and criticisms during the pursuit of this research.

REFERENCES

Bard, P. A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system. *Amer. J. Physiol.*, 1928, *84:* 490–515.

Bard, P., and Rioch, D. McK. A study of four ca's deprived of neocortex and additional portions of the forebrain. *Johns Hopk. Hosp. Bull.*, 1937, *60:* 73–148.

Bouillaud, J. Recherches expérimentales sur les fonctions du cerveau (lobes cérébraux) en général, et sur celles de sa portion antérieure en particulier. *J. Physiol. exp. path.*, 1830, *10:* 36–98.

Broca, P. Remarques sur le siège de la faculté du langage articulé; suivies d'une observation d'aphémie (perte de la parole). *Bull. Soc. anat. Paris.*, 1861–63, *36:* 330–357.

BUCY, P. C., and FULTON, J. F. Ipsilateral representation in the motor and premotor cortex of monkeys. *Brain*, 1933, *56:* 318–342.

DANDY, W. E. Physiological studies following extirpation of the right cerebral hemisphere in man. *Johns Hopk. Hosp. Bull.*, 1933, *53:* 31–51.

DELAVAN, D. B. On the localization of the cortical motor centre of the layrnx. *Med. Rec. N. Y.*, 1885, *27:* 178–179.

DUSSER DE BARENNE, J. G. Recherches expérimentales sur les fonctions du système nerveux central, faites en particulier sur deux chats dont le néopallium avait été enlevé. *Arch. néerl. Physiol.*, 1920, *4:* 31–123.

FOERSTER, O. The motor cortex in man in the light of Hughlings Jackson's doctrines. *Brain*, 1936, *59:* 135–159.

FULTON, J. F., and DUSSER DE BARENNE, J. G. The representation of the tail in the motor cortex of primates, with special reference to spider monkeys. *J. cell. comp. Physiol.*, 1933, *2:* 399–426.

FULTON, J. F., and KELLER, A. D. *The sign of Babinski. A study of the evolution of cortical dominance in primates.* Springfield, Ill., Charles C Thomas, 1932, xii, 168 pp.

GARDNER, W. J. Removal of the right cerebral hemisphere for infiltrating glioma. *J. Amer. med. Ass.*, 1933, *101:* 823–826.

GOLTZ, F. Der Hund ohne Grosshirn. Siebente Abhandlung über die Verrichtungen des Grosshirns. *Pflüg. Arch. ges. Physiol.*, 1892, *51:* 570–614.

GRINKER, R. R. *Neurology.* Springfield, Ill., Charles C Thomas, 1934, ix, 975 pp.

GRÜNBAUM, A. S. F., and SHERRINGTON, C. S. Observations on the physiology of the cerebral cortex of the anthropoid apes. *Proc. roy. Soc.*, 1903, *72:* 152–155.

HAMBOURGER, W. E. Excitant action of morphine on the long-surviving decorticated cat. *Proc. Soc. exp. Biol. N. Y.*, 1937, *36:* 36–38.

HOFF, E. C. Corticospinal fibers arising in the premotor area of the monkey. *Arch. Neurol. Psychiat. Chicago*, 1935, *33:* 687–697.

HOFF, E. C., and HOFF, H. E. Spinal terminations of the projection fibres from the motor cortex of primates. *Brain*, 1934, *57:* 454–474.

HORSLEY, V. The Linacre Lecture on the function of the so-called motor area of the brain. *Brit. med. J.*, 1909, *2:* 125–132.

JELLIFFE, S. E., and WHITE, W. A. *Diseases of the nervous system, a text book of neurology and psychiatry.* 6th ed. Philadelphia, Lea & Febiger, 1935, 1175 pp.

KARPLUS, J. P., and KREIDL, A. Über Totalexstirpationen einer und beider Grosshirnhemisphären an Affen (Macacus rhesus). *Arch. Anat. Physiol.*, 1914, (Physiol. Abt.), 155–212.

KENNARD, MARGARET A. Corticospinal fibers arising in the premotor area of the monkey. *Arch. Neurol. Psychiat., Chicago*, 1935, *33:* 698–711.

LEYTON, A. S. F., and SHERRINGTON, C. S. Observations on the excitable cortex of the chimpanzee, orang-utan and gorilla. *Quart. J. exp. Physiol.*, 1917, *11:* 135–222.

LLOYD, J. H., and DEAVER, J. B. A case of focal epilepsy successfully treated by trephining and excision of the motor centres. *Amer. J. med. Sci.*, 1888, *96:* 477–487.

MAGOUN, H. W., RANSON, S. W., and FISHER, C. Corticifugal pathways for mastication, lapping and other motor functions in the cat. *Arch. Neurol. Psychiat., Chicago*, 1933, *30:* 292–308.

NANCREDE, C. B. Two successful cases of brain surgery. *Med. News, Phila.*, 1888, *53:* 584–588.

OGDEN, R., and FRANZ, S. I. On cerebral motor control: the recovery from experimentally produced hemiplegia. *Psychobiol.*, 1918, *1:* 33–59.

RANSON, S. W. Some functions of the hypothalamus. *Harvey Lectures*, 1937, *32:* 92–121.

ROTHMANN, M. Der Hund ohne Grosshirn. *Dtsch. Z. Nervenheilk.*, 1910, *38:* 267–269.

ROTHMANN, M. Zusammenfassender Bericht über den Rothmannschen grosshirnlosen Hund nach klinischer und anatomischer Untersuchung. *Z. ges. Neurol. Psychiat.*, 1923, *87:* 247–313.

WALKER, A. E., and GREEN, H. D. Electrical excitability of the motor face area: a comparative study in primates. *J. Neurophysiol.*, 1938, *1:* 152–165.

WECHSLER, I. S. *A text book of clinical neurology.* 3rd ed. Philadelphia, W. B. Saunders Co., 1935, 826 pp.

ZELIONY, G.-P. Observations sur des chiens auxquels on a enlevé les hémisphères cérébraux. *C. R. Soc. Biol., Paris*, 1913, *74:* 707–708.

CELL-CHANGES IN SOME OF THE HYPOTHALAMIC NUCLEI IN EXPERIMENTAL FEVER

L. O. MORGAN
The Department of Anatomy, University of Cincinnati, College of Medicine
Cincinnati, Ohio

(Received April 18, 1938)

SEVERAL investigators have produced evidence to show that the hypothalamus plays an important role in the regulation of body temperature (Isenschmidt and Krehl;[1] Jakoby and Roemer;[2] Reichard;[3] Glaser;[4] Citrone and Leschke;[5] Barbour and Wing;[6] Morgan and Johnson;[10] Keller and Hare;[11] Bazett, Alpers and Erb;[12] Ranson and Ingram;[13] Frazier, Alpers and Lewy,[14] and others). However it has not yet been shown which nuclei of the hypothalamus are concerned with temperature regulation. Likewise the manner in which these nuclei influence body temperature and the physiological mechanisms involved are as yet not definitely understood.

The physiology of temperature regulation has been reviewed by Barbour.[15] The adrenal and thyroid glands and the hypophysis are believed to influence body temperature. Carbohydrate, protein and fat metabolism, the rate of evaporation of water from the body, peripheral vasomotor changes, changes in water and salt balance, water shifting and changes in blood sugar are believed to play an important role in regulating body temperature. The relationship of vegetative centers in the hypothalamus to several of these functions has been discussed in a previous paper.[16] The significance of this relationship to the regulation of body temperature has been discussed by Davison and Selby.[17]

It has been previously pointed out[18] that in mammals the cells of the nuclei of the hypothalamus are so intermingled that it is virtually impossible to place an experimental lesion in a single nucleus without causing injury to one or more adjacent cell groups. Furthermore our knowledge of the fiber connections in and through this region is not sufficient to preclude the possible effects of injury to fiber tracts when placing lesions in this area. The present investigation was undertaken with the hope that a fever producing substance such as typhoid toxin, might set up a reaction in the temperature regulating centers of the brain to the extent that the cells involved would show cytological alterations.

METHODS

Fifteen dogs and four rabbits were used in this series of experiments. The procedure consisted essentially in producing an experimental hyperthermia by the injection of typhoid or bronchisepticus toxin. In all but two cases, typhoid toxin was used. The toxins were prepared for me from killed cultures of bacteria by Drs. Eddy and Howard in the Department of Bacteriology. The typhoid toxin was much stronger than the preparations commonly used for producing immunity in the human. Hypodermic injections were used in all but four cases. In these four animals (Nos. 10–13) the toxin was injected into a vein.

The number of injections, the amount of toxin injected, and the period of time during which the injections were continued was varied considerably with different animals. Temperatures were taken by rectum with a clinical thermometer. One or more temperature readings were taken at frequent intervals for a period of hours after the injection until the temperature had risen and then returned to normal.

The accompanying table gives a summary of the most important data concerning the experimental procedure. The maximum rise in temperature recorded in the table represents the maximum rise in temperature which occurred after any single injection of toxin. The data indicate that rabbits are sensitive to much smaller doses of toxin, in proportion to body weight, than are dogs. It will also be noted that 0.6 cc. of toxin injected intravenously (cases 10–13) produced a greater rise in temperature in dogs than was usually obtained by a hypodermic injection of 4–10 cc.

A few hours after the last injection the animal was killed and the brain removed. The brain stem was embedded in celloidin and cut into sections 35 microns in thickness. These

Table I—Summary of Experiments

Animal Number	*Size of Animal*	*Total of Toxin Injected*	*Number of Injections*	*Duration of Experiment*	*Maximum Rise in Temperature*	*Percentage of Chromatolytic Cells*		
						Nucleus Tuberomamm	*Basal Optic Ganglia*	*Nucleus Paraventricularis*
Dog 1	Small	16.5 cc.	5	72 hrs.	2.0°F.	50	14	13
Dog 2	Small	11.5 cc.	4	24 hrs.	2.2°F.	68	12	11
Dog 3	Large	20 cc.	4	24 hrs.	2.5°F.	56	22	18
Dog 4	Medium	15 cc.	4	24 hrs.	3.4°F.	57	0	0
Dog 5	Medium	21 cc.	4	24 hrs.	4.3°F.	51	20	12
Dog 6	Small	19 cc.	2	12 hrs.	1.2°F.	68	32	20
Dog 7	Large	23 cc.	2	12 hrs.	2.6°F.	68	9	8
Dog 8	Medium	24 cc.	2	12 hrs.	2.1°F.	66	6	6
Dog 9	Small	22 cc.	2	12 hrs.	3.8°M.	50	8	8
Dog 10	Medium	2.7 cc. intraven.	5	53 hrs.	5.2°F.	74	13	12
Dog 11	Medium	2.9 cc. intraven.	5	54 hrs.	4.0°F.	62	23	19
Dog 12	Medium	3.8 cc. intraven.	6	101 hrs.	3.2°F.	73	30	23
Dog 13	Large	3.8 cc. intraven.	6	101 hrs.	4.5°F.	33	12	12
Rabbit 14	Large	0.7 cc.	2	13 hrs.	4.5°M.	75	0	0
Rabbit 15	Large	1 cc.	2	14 hrs.	5.4°F.	77	—	—
Rabbit 16	Large	0.4 cc.	1	12 hrs.	1.7°F.	60	10	10
Rabbit 17	Large	0.4 cc.	1	10 hrs.	1.5°F.	56	0	0
Dog 18	Large	10 cc. B.Bronch.	2	7 hrs.	4.1°F.	54	0	0
Dog 19	Large	16 cc.	2	23 hrs.	2.0°F.	43	10	5
				Average		60	15.8	12.6

sections were stained by a modified iron hematoxylin technique (Morgan)[16]. The sections were studied with the object of determining whether the toxins injected produced histological changes in any of the cell groups of the brain stem. In four cases a study was made of the entire brain stem from the caudal end of the medulla to the optic chiasma. In the remaining cases particular attention was given only to the region of the third ventricle, corpus striatum, thalamus, hypothalamus, epithalamus and mid-brain. The twenty brains previously used for a study of the normal histology of the hypothalamus in the dog (Morgan)[18] were used as controls.

Results

In so far as chromatolysis of nerve cells can be taken as a criterion, it is apparent that typhoid and bronchisepticus toxins have a selective action upon three cell groups all of which are located in the region of the third ventricle. The three cell groups which show definite chromatolytic changes are the nucleus tuberomammillaris (mammillo-infundibularis), the basal optic ganglia

(nucleus supra-opticus), and the nucleus paraventricularis. I have described and illustrated these cell groups in the brain of the dog in a previous paper,[18] and pointed out the differences in distribution of these cell groups in the dog, the albino rat, and the human.

The nucleus tubero-mammillaris is composed of large cells most of which are grouped around the fornix from the level of the optic chiasma to the mammillary bodies. The cells increase in number as we pass from the chiasma toward the mammillary bodies and smaller groups of cells are placed along the base of the tuber cinereum. The basal optic ganglia consist of large cells which

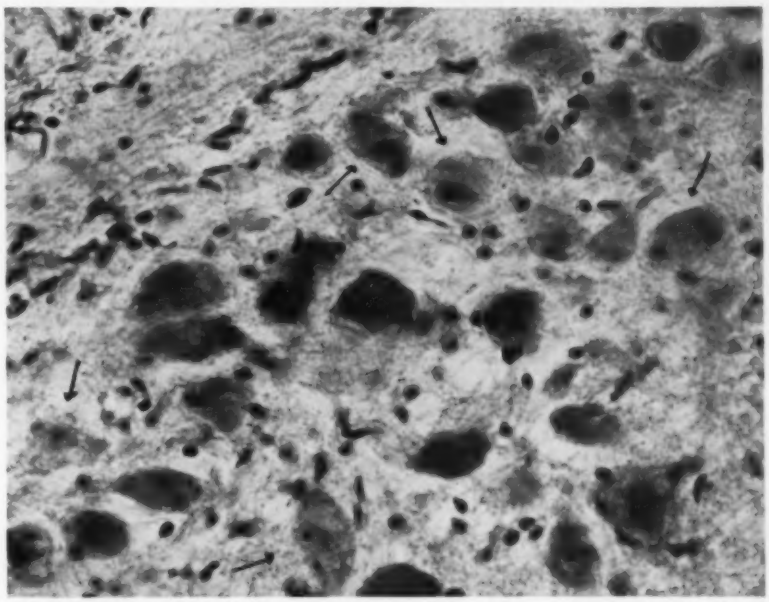


FIG. 1. Photograph of a portion of the nucleus tubero-mammillaris (case 2) illustrating the cell changes which occur with experimental fever. The arrows indicate chromatolytic cells.

begin at the optic chiasma and extend for a short distance along the optic tracts. The nucleus consists essentially of two parallel columns of cells. The larger of these columns is placed along the dorsal portion of the oro-lateral surface of the optic tract. The second group of cells follow the caudo-medial border of the optic tract. The paraventricular nucleus is composed of large cells arranged in a column whose axis is almost perpendicular to that of the basal optic ganglion. This cell group begins near the oral end of the basal optic ganglion and extends upward and orally through the wall of the third ventricle toward the anterior commissure.

That the nucleus tubero-mammillaris, basal optic ganglia, and nucleus paraventricularis are quite sensitive to typhoid and bronchisepticus toxins, is indicated by the fact that one or two injections of these toxins is capable of producing marked chromatolysis in these cell groups within a few hours' time.

On the other hand, it is of interest to note that in those cases in which a larger number of injections was made over a longer period of time, there is no significant difference in the amount of chromatolysis.

The nucleus tubero-mammillaris was involved in every case and to a greater degree than either the basal optic ganglia or the nucleus paraventricularis. The number of cells in this nucleus which were definitely chromatolytic varied from 33 to 77 per cent (Fig. 1).

In many cases there is a striking similarity in the amount of chromatolysis found in the basal optic ganglia and the paraventricular nucleus. In those cases where there is a difference the basal optic ganglia are affected to a greater degree. In four cases neither of these nuclei possessed any cells which appeared definitely chromatolytic. In five cases 10 per cent or less of the cells were chromatolytic. The highest percentage of chromatolysis found in any case was 32 per cent for the basal optic ganglia and 23 per cent for the nucleus paraventricularis.

When we take an average of the amount of chromatolysis found in each cell group throughout the series of experiments the average number of chromatolytic cells in the nucleus tubero-mammillaris is 60 per cent of the total, for the basal optic ganglia 15.8 per cent, and for the nucleus paraventricularis there was an average of 12.6 per cent showing chromatolysis. Many cells showed variations from the normal appearance sufficient to suggest a tendency toward chromatolysis but unless the cell was definitely chromatolytic it was considered as normal.

An attempt was made to determine the role of the thyroids in producing hyperthermia in those animals injected with toxin. In seven of these cases the blood supply to the thyroids was clamped while the temperature was elevated. These animals were etherized and several readings taken until the temperature became stable. When the thyroids were clamped off the temperature fell rapidly. In a few cases the temperature fell to normal or below, but in most cases the temperature did not return entirely to normal. While these experiments indicate that the thyroids play some role in the production of hyperthermia in these cases there are apparently other factors involved. In rabbits Nos. 16 and 17 the thyroid glands were removed three days before the toxin was injected.

The evidence obtained from this investigation points to the nucleus tubero-mammillaris as playing an important role in the producing hyperthermia. The paraventricular nucleus and basal optic ganglia are implicated to a more variable and a lesser degree. However, the regulation of body temperature is so inseparably linked up with other somatic and vegetative functions that it is doubtful if we are justified at present in assuming the presence in the brain of a center which is solely concerned with the regulation of body temperature. If such a center exists it is probably closely associated with various vegetative centers in the hypothalamus thus utilizing several older, well established mechanisms which serve other functions in addition to playing a role in the regulation of body temperature.

Summary

The entire brain stem was studied in 15 dogs and 4 rabbits following an experimental fever produced by either a hypodermic or intravenous injection of either typhoid or bronchisepticus toxin.

Significant cell changes were noted only in three nuclei of the hypothalamus.

The nucleus tubero-mammillaris was involved in every case. An average of 60 per cent of the cells in this nucleus showed definite chromatolytic change.

A variable amount of chromatolysis was found in the paraventricular nucleus and the basal optic ganglia in 14 of the 19 animals studied. The average number of chromatolytic cells in these cases was 15.8 per cent for the paraventricular nucleus and 12.6 per cent for the basal optic ganglia.

REFERENCES

1. Isenschmid, R., and Krehl, L. Über den Einfluss des Gehirns auf die Wärmeregulation, *Arch. exp. Path. Pharmak.*, 1912, *70:* 109–134.
2. Jacobj, C., and Roemer, K. Beitrag zur Erklärung der Warmestichyperthermie, *Arch. exp. Path. Pharmak.*, 1912, *70:* 149–182.
3. Reichardt, M. Über die Störungen der Körpertemperatur und der vasomotorisch-trophischen Funktionen bei Hirnkranken, *Z. ges. Neurol. Psychiat.*, 1913, *18:* 417–427.
4. Glaser, W. Beitrag zur Kenntnis des cerebralen Fiebers, Z. *ges. Neurol. Psychiat.*, 1913, *17:* 493–499.
5. Citrone, J., and Leschke, E. Ueber den Einfluss der Ausschaltung des Zwischenhirns auf das infectiöse und nichtinfectiöse Fieber. *Z. exp. Path. Pharmak.*, 1913, *14:* 379–390.
6. Barbour, H. G., and Wing, E. S. The direct application of drugs to the temperature centers. *J. Pharmacol.*, 1913, *5:* 105–147.
7. Isenschmid, R., and Schnitzler, W. Beitrag zur Lokalisation des Wärmeregulation vorstehenden Zentralapparates im Zwischenhirn. *Arch. exp. Path. Pharmak.*, 1914, *76:* 202–223.
8. Walbaum, H. Hirnbefunde an durch Hirnreizung hyperthermisch gemachten Kaninchen und ihre Beziehungen zur Hyperthermie. *Arch. exp. Path. Pharmak.*, 1914, *75:* 423–434.
9. Högner, P. Die klinischen Erscheinungen bei Erkrankungen des 3. Gehirnventrikels und seiner Wandungen. *Dtsch. Z. Nervenheilk.*, 1927, *97:* 238–266. (Abstr. *Arch. Neurol. Psychiat.*, 1929, *21:* 191.)
10. Morgan, L. O., and Johnson, C. A. Experimental lesions in the tuber cinereum of the dog. *Arch. Neurol. Psychiat., Chicago*, 1930, *24:* 696–726.
11. Keller, A. D., and Hare, W. K. The hypothalamus and heat regulation. *Proc. Soc. exp. Biol., N. Y.*, 1932, *29:* 1069–1070.
12. Bazett, H. C., Alpers, B. J., and Erb, W. H. Hypothalamus and temperature control. *Arch. Neurol. Psychiat., Chicago*, 1933, *30:* 728–748.
13. Ranson, S. W., and Ingram, W. R. Hypothalamus and regulation of body temperature. *Proc. Soc. exp. Biol., N. Y.*, 1935, *32:* 1439–1441.
14. Frazier, C. H., Alpers, B. J., and Lewy, F. H. The anatomical localization of the hypothalamic centre for the regulation of temperature. *Brain*, 1936, *59:* 122–134.
15. Barbour, H. G. The heat-regulating mechanism of the body. *Physiol. Rev.*, 1921, *1:* 295–326.
16. Morgan, L. O. The nuclei of the region of the tuber cinereum. *Arch. Neurol. Psychiat., Chicago*, 1930, *24:* 267–299.
17. Davison, C., and Selby, N. E. Hypothermia in cases of hypothalamic lesions. *Arch. Neurol. Psychiat., Chicago*, 1935, *33:* 570–591.
18. Morgan, L. O. Cell groups in the tuber cinereum of the dog, with a discussion of their function. *J. comp. Neurol.*, 1930, *51:* 271–297.

TABLE OF CONTENTS

Vol. 1, No. 3

JOURNAL OF NEUROPHYSIOLOGY

1. LORENTE DE NÓ, RAFAEL. Limits of Variation of the Synaptic Delay of Motoneurons 187

2. LORENTE DE NÓ, RAFAEL. Synaptic Stimulation of Motoneurons as a Local Process 195

3. LORENTE DE NÓ, RAFAEL. Analysis of the Activity of the Chains of Internuncial Neurons 207

4. CASE, J. THEODORE, AND PAUL C. BUCY. Localization of Cerebral Lesions by Electro-encephalography 245

5. GREEN, HAROLD D., AND A. EARL WALKER. The Effects of Ablation of the Cortical Motor Face Area in Monkeys 262

6. MORGAN, L. O. Cell-Changes in Some of the Hypothalamic Nuclei in Experimental Fever 281